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Raffaele Brustia

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Raffaele Brustia. Etude de l'impact d'un programme de Récupération Amélioré en Transplantation Hépatique. Médecine humaine et pathologie. Université de Picardie Jules Verne, 2021. Français. NNT : 2021AMIE0092 . tel-03965666

HAL Id: tel-03965666

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Thèse de Doctorat

Mention BIOLOGIE SANTE

Spécialité PHYSIOPATHOLOGIE HUMAINE

Présentée à ***l'École Doctorale en Sciences Technologie et Santé (ED 585)***

De l'Université de Picardie Jules Verne

par

Raffaele BRUSTIA

Pour obtenir le grade de Docteur de l'Université de Picardie Jules Verne

Étude de l'impact d'un programme de Récupération Amélioré en Transplantation Hépatique

Soutenue le 15/12/2021 après avis des rapporteurs, devant le jury d'examen présidé par le Professeur François FAITOT:

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REMERCIEMENTS

A l'ensemble des équipes de professionnels de santé des Hôpitaux Universitaires de la Pitié Salpetrière à Paris, travaillant autour de la transplantation hépatique et ayant permis la réalisation de ce projet de recherche, et également à l'Unité de recherche pour la Simplification des Soins chez les Patients Chirurgicaux Complexes (SSPC) de l'Université de Picardie – Jules Verne (UPJV) pour l'accompagnement méthodologique.

Un remerciement particulier à l'ensemble des membres du jury de cette thèse pour leur bienveillance – le Président en particulier – et pour leurs commentaires constructifs.

L'ensemble de ces travaux est dédié aux patients en attente d'une transplantation hépatique, dans l'espoir d'une amélioration de leur prise en charge.

SOMMAIRE

1 LISTE DES ABBREVIATIONS 4

2 JUSTIFICATION SCIENTIFIQUE DE LA RECHERCHE 5

2.1 INTRODUCTION GENERALE 5

2.2 LE PARCOURS DE SOINS COMME INNOVATION ORGANISATIONNELLE 5

2.3 RECUPERATION AMELIOREE APRES CHIRURGIE 8

2.3.1 CONCEPT ET DEFINITION 8

2.3.2 CONNAISSANCES EN RAC 8

2.3.3 RATIONNEL DE LA RAC 10

2.4 LA TRANSPLANTATION HEPATIQUE 23

2.4.1 INDICATIONS 24

2.4.2 BILAN PRE-TRANSPLANTATION 25

2.4.3 TYPE DE DONNEURS ET GREFFONS 30

2.4.4 TRANSPLANTATION HEPATIQUE (ACTE CHIRURGICAL) 32

2.4.5 TRANSPLANTATION HEPATIQUE (CONSIDERATIONS ANESTHESIOLOGIQUES) 36

2.4.6 LA GESTION POSTOPERATOIRE PRECOCE APRES TRANSPLANTATION HEPATIQUE. 40

2.4.7 LA TRANSPLANTATION HEPATIQUE COMME PARCOURS DE SOINS COMPLEXE 41

2.4.8 PRISE EN CHARGE HABITUELLE DE LA PERIODE PERI-OPERATOIRE D'UNE TRANSPLANTATION HEPATIQUE. 42

3 PROJET DE RECHERCHE : LA RAC EN TRANSPLANTATION HEPATIQUE 44

3.1 HYPOTHESES DE LA RECHERCHE 44

3.2 EVALUATION DE L'INNOVATION EN CHIRURGIE 44

3.3 ETAPES DE LA RECHERCHE SUR LA RAC EN TRANSPLANTATION HEPATIQUE 47

4 TRAVAUX DE RECHERCHE 51

4.1.1 PREMIERE PHASE : LA PREUVE DE CONCEPT 52

4.1.2 DEUXIEME PHASE : LES CRITERES DE JUGEMENT 53

4.1.3 TROISIEME PHASE: RECOMMENDATIONS SUR LA RAC en TRANSPLANTATION HEPATIQUE 58

5 CONCLUSIONS 60

6 BIBLIOGRAPHIE 61

7 LISTE DES FIGURES 77

8 ANNEXES 79

9 RESUME – ABSTRACT 158

1 LISTE DES ABBREVIATIONS

ABBREVIATION	DEFINITION
AFP	Alphafoetoprotéine
CHC	Carcinome hépatocellulaire
CJ	Critères de jugement
DMS	Durée moyenne de séjour
EHPAD	Établissements d'hébergement pour personnes âgées dépendantes
ERAS	Enhanced recovery after surgery.
ERC	Essai randomisé contrôlé
ESPEN	European Society of Parenteral and Enteral Nutrition
ETO	Échographie trans œsophagienne
GR	Globules rouges
HAD	Hospitalisation à domicile
HPB	Hépato-bilio-pancréatique
ILTS	International liver transplantation society
IMS	Indication Médicale de sortie
IPA	Infirmier(e) de pratiques avancées
ISO	Infection du site opératoire
IV	Intraveineux
MELD	Model for end stage liver disease
NE	Nutrition entérale
NP	Nutrition parentérale
PAM	Pression artérielle moyenne
PCA	Patient controlled analgesia
PFC	Plasma frais congelé
PONV	Nausées et vomissements postopératoires
PREPS	Programmes de recherche sur la performance du système de soins
PVC	Pression veineuse centrale
RAC	Récupération améliorée après chirurgie
SSR	Soins de suite et de réadaptation
TH	Transplantation hépatique
USC	Unité de soins continus
USLD	Unité de soins de longue durée
VHB	Virus de l'hépatite B
VHC	Virus de l'hépatite C

2 JUSTIFICATION SCIENTIFIQUE DE LA RECHERCHE

2.1 INTRODUCTION GENERALE

L'ensemble de ce travail de recherche repose sur l'hypothèse qu'un protocole de RAC appliqué à la TH pourrait améliorer la prise en charge des malades notamment en termes de suites post-opératoires et de durée de séjour/récupération fonctionnelle.

L'hypothèse de travail se base sur les trois éléments suivants :

- Le parcours de soin lié à la TH est un parcours chirurgical complexe[1,2], nécessitant une mobilisation importante de ressources humaines et financières, imposant l'intervention pluridisciplinaire et constante de chirurgiens, d'anesthésiste-réanimateurs, d'hépatologues, d'infirmiers, kinésithérapeutes, diététiciens et psychologues, avant, pendant et après la TH. Tous ces éléments sont essentiels et conditionnent les résultats à court terme.
- Le programme de RAC est un protocole de soins fondé sur la réduction de la réponse au stress chirurgical et l'amélioration de la récupération : le programme se structure sur un ensemble de mesures pré, per et postopératoires[3–6]. L'applicabilité du concept de RAC a été démontrée dans plusieurs types de chirurgies complexes et notamment en chirurgie hépatobiliaire[7], qui se rapproche le plus de la transplantation hépatique.
- Lors des phases de planification de ce travail de recherche, aucune publication n'avait jamais été réalisée dans ce domaine.

2.2 LE PARCOURS DE SOINS COMME INNOVATION ORGANISATIONNELLE

L'innovation désigne l'introduction d'un produit ou d'un procédé nouveau ou significativement amélioré par rapport à l'existant. Plus précisément, l'innovation portant sur des procédés concerne - entre autres - la production et les méthodes de développement, la logistique et la distribution, le système d'information et de communication, l'organisation des procédures, l'organisation du travail.

Concernant l'innovation en santé, au-delà des thérapies géniques et des biotechnologies, voici quelques exemples qui en font partie [8,9]:

- **les technologies innovantes** (la robotique chirurgicale, les objets de santé connectés, l'information des patients, solutions thérapeutiques de e-santé, la télémédecine …).

- les comportements (**éducation thérapeutique**, patient connecté, solutions de e-santé…).

- **les nouvelles organisations des prises en charge**, des parcours (nouveaux modes d'exercice et de prise en charge, **parcours de soins**, dossier médical partagé, plateformes de suivi à distance…).

Les nouvelles organisations en santé ont pour objectif d'améliorer la coordination des différents intervenants médicaux et paramédicaux et de moderniser le système de soins. Des plans de financement ciblant spécifiquement la « médecine de parcours »[10] ont même émergé depuis 2015 à l'échelle nationale dans le cadre de la politique de santé et de modernisation du système de soins.

Au sein de ces « parcours », trois niveaux sont identifiés :

- **les parcours de santé**, qui articulent les soins avec, en amont, la prévention en santé et sociale et, en aval, l'accompagnement médico-social, le maintien et le retour à domicile.

- **les parcours de soins**, qui permettent l'accès aux consultations de premier recours et, quand cela est nécessaire, aux autres lieux de soins : hospitalisation programmée ou non (urgences), hospitalisation à domicile (HAD), soins de suite et de réadaptation (SSR), unité de soins de longue durée (USLD) et établissements d'hébergement pour personnes âgées dépendantes (EHPAD).

- **Les parcours de vie**, qui envisagent la personne dans son environnement : famille et entourage, scolarisation, prévention de la désinsertion professionnelle, réinsertion, logement…

Les nouvelles organisations en santé qui participent à améliorer le parcours des patients, et par conséquent l'efficience du système de santé, relèvent du champ de l'innovation au même titre que le séquençage génomique, la chirurgie robotique ou l'application de l'intelligence artificielle en santé. L'ancien paradigme de la recherche réalisée exclusivement dans un laboratoire de sciences fondamentales ne représente qu'une petite fraction de l'innovation en santé, et en particulier dans le domaine de la

chirurgie[11]. L'innovation porte également sur les modifications des systèmes de santé et les indicateurs de performance, comme par exemple le parcours de soins et la mesure de la qualité des soins. En effet, l'intervention chirurgicale en soi n'est qu'une partie du traitement dont relèvent certains patients. Les soins médicaux appropriés en pré, intra et postopératoire (regroupés sous le nom de médecine peropératoire) font partie intégrante de la prise en charge chirurgicale, dont ils sont indissociables.

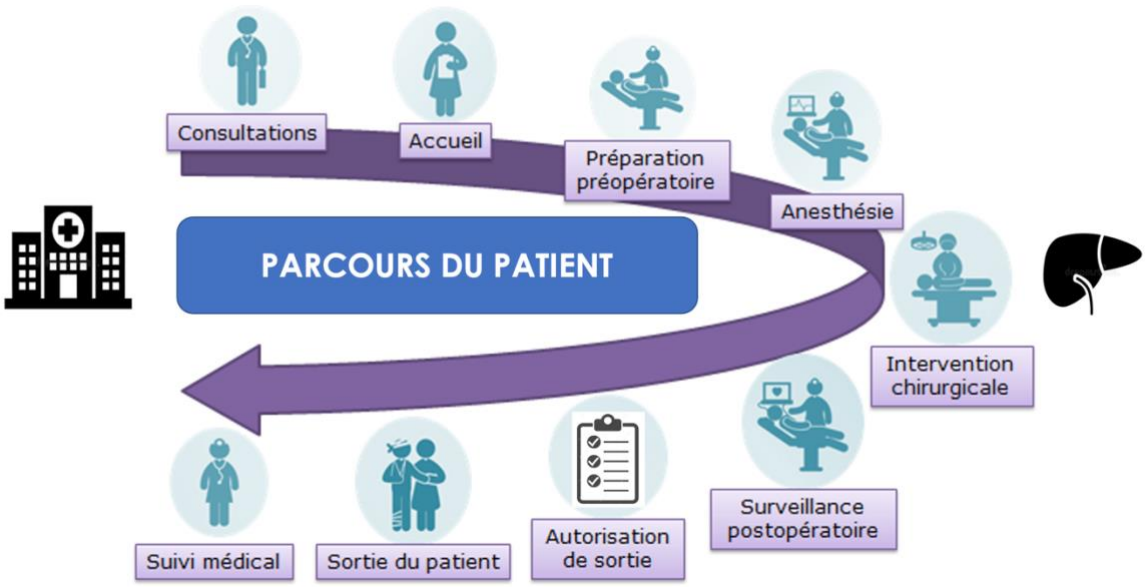


***Figure 1**. Représentation schématique des principales étapes du parcours d'un patient au cours d'une hospitalisation en vue d'une intervention chirurgicale.*

La transplantation hépatique représente « le » modèle ultime d'une nécessaire coordination, d'une prise en charge multidisciplinaire, de la complexité des soins techniques, de l'éducation thérapeutique et de la prise en charge médico-sociale. Ainsi, apporter une nouvelle forme de prise en charge innovante en transplantation parait intéressante et aurait probablement un impact significatif. Parmi ces innovations, la récupération améliorée après chirurgie est une des solutions à apporter.

2.3 RECUPERATION AMELIOREE APRES CHIRURGIE

2.3.1 CONCEPT ET DEFINITION.

Le concept du programme de Récupération Améliorée après Chirurgie (RAC) (autrement dit *Fast Track* ou *Enhanced Recovery After Surgery* - ERAS) est un protocole de soins, dont les modalités sont issues des données de la littérature, et dont les buts sont de réduire le stress chirurgical, d'améliorer la récupération, de réduire le taux de complications post-opératoires et la durée moyenne de séjour (DMS). Il repose sur 3 éléments fondamentaux :

1. une approche multimodale des modifications des protocoles de soins pré-, per- et post-opératoires,
2. la résolution des obstacles à la récupération post-opératoire grâce à une équipe multidisciplinaire active qui travaille en collaboration autour du patient et ce, tout au long du parcours de soin (chirurgien, anesthésiste-réanimateur, infirmier(e) de coordination, kinésithérapeutes, psychologues, diététiciens, nutritionnistes)
3. un réajustement permanent et périodique des modalités du programme de soins basé sur la réalisation d'audits réguliers[3,4,12,13].

Les éléments clés de l'approche multimodale comprennent une information exhaustive pré-opératoire du patient, une anesthésie avec des agents anesthésiques de courte durée d'action permettant une extubation précoce, l'utilisation limitée de cathéters, de sondes et de drains, une analgésie multimodale optimisée, ainsi qu'une mobilisation active et une réalimentation entérale précoces[3,4,12,13].

2.3.2 CONNAISSANCES EN RAC

Le concept de « Fast-Track » a été décrit pour la première fois au cours d'un projet clinique visant à améliorer les résultats de la chirurgie du pontage aorto-coronarien : l'ensemble des traitements périopératoires regroupés sous ce nom a été publié en 1994[14]. Cette étude a montré une réduction de la durée de séjour en unité de soins intensifs d'environ 20% sur les 280 patients inclus. Un an plus tard, et en se basant sur les mêmes principes d'optimisation périopératoire, une équipe de chirurgie digestive danoise[15] a rapporté une réduction significative du temps de récupération chez 8 patients âgés et à haut risque, permettant une sortie à J2 après résection sigmoïdienne. Cette publication a été suivie d'une deuxième série focalisant sur 16 patients[16], toujours par la même équipe, confirmant une récupération rapide après résection sigmoïdienne grâce à une approche multimodale. Les éléments de base

reposaient sur l'anesthésie péridurale thoracique comme moyen pour contrôler la douleur, améliorer la mobilité, et réduire l'iléus postopératoire. En parallèle, d'autres équipes ont abordés les soins périopératoires sur le plan endocrinien et métabolique. Cette approche incluait les rôles d'acides aminés spécifiques en nutrition périopératoire[17], des protéines de la réaction inflammatoire et le métabolisme chez les patients chirurgicaux atteints de cancer[18] et la préparation métabolique par le biais d'une boisson glucidique préopératoire pour éviter les effets du jeûne[19].

L'ensemble des travaux se sont rapidement orientés sur l'amélioration de la récupération et la réduction du taux de complications par la modification de la réponse métabolique à une agression chirurgicale, plutôt que de simplement limiter la durée du séjour. Dans cette perspective, le concept a évolué de « Fast-Track », (plutôt évocateur de courte durée de séjour, sur des patients sélectionnés) vers « ERAS » (Enhanced Recovery After Surgery) : **le point clé final est la qualité, plutôt que la vitesse, de la récupération après chirurgie.**

Les éléments « type » d'un programme RAC sont le conseil préopératoire, la supplémentation glucidique préopératoire, la nutrition périopératoire, l'absence d'utilisation systématique de drains chirurgicaux, la prophylaxie de la thromboembolie, la prophylaxie antibiotique, l'approche mini-invasive, la gestion ciblée des liquides en peropératoire, l'analgésie multimodale, la prévention de l'hypothermie, une alimentation per os précoce, contrôle glycémique, prévention de la gastroparésie, mobilisation précoce, prévention des nausées et vomissements postopératoires et audits systématiques. L'ensemble du programme est resumé par le tableau ci-dessous.

PREOPERATOIRE	PEROPERATOIRE	POSTOPERATOIRE
Informations au patient	Antibioprophylaxie	Thromboprophylaxie - Compression pneumatique
Suppléments nutritifs	Prévention de l'hypothermie peropératoire	Drainage vésical retirée fin chirurgie
Immunonutrition	Voie d'abord chirurgicale	Sonde gastrique retirée fin chirurgie
Pas de Prémédication	Analgésie multimodale pérop	Prévention de l'iléus postopératoire
Jeûne préopératoire limité	Remplissage optimisé-monitorage	Analgésie postopératoire multimodale
Apport de solutions (d'hydrates de carbone) sucrées orales	Prévention des Nausées et Vomissement post opératoires (NVPO)	Mobilisation avant 24h
	Pas de drainage abdominal (max 48h)	Réalimentation avant 24h
	Corticoïdes	

Figure2 *Eléments d'un programme RAC générique*

Une note concernant la nomenclature francophone : une certaine confusion a régné pendant quelques années sur la traduction la plus juste des termes « fast-track » et ERAS. C'est pour cela qu'il est encore possible de retrouver les acronymes RRAC (Récupération/Réhabilitation Rapide Après Chirurgie) ou RAAC (Récupération/Réhabilitation Accélérée Après Chirurgie). Cependant, la traduction la plus proche et fidèle est probablement RAC (Récupération Améliorée après Chirurgie)[20].

Le premier protocole le plus complet focalisé sur la chirurgie colorectale, a été développé et publié en 2001[5]. Le concept reposait sur plusieurs composantes : une équipe multidisciplinaire travaillant ensemble autour du patient; une approche multimodale pour résoudre les problèmes qui retardent la récupération et à l'origine des complications; une approche scientifique et factuelle aux protocoles de soins; enfin un changement de management avec des outils d'audit interactif. La pertinence d'un tel protocole de soins a été mis en avant par une étude multicentrique européenne, suggérant comme **les soins peropératoires plutôt que l'acte chirurgical à proprement parler, puissent dicter les résultats à court terme**[21].

Pour résumer, un programme de RAC se structure sur un ensemble de mesures pré, per et postopératoires, visant la réduction de la réponse au stress chirurgical et l'amélioration de la récupération. Aucun élément à lui seul ne peut améliorer les suites d'une intervention : la clé repose sur la synergie et l'enchainement des éléments du programme, les uns après les autres[3–5].
Pour obtenir des résultats solides sur la durée, il est nécessaire que l'équipe multidisciplinaire travaillant autour du patient puisse avoir une vision complète du parcours de soins et des résultats, avec des réajustements périodiques par des audits réguliers[3–5].

2.3.3 RATIONNEL DE LA RAC

En effet, la période postopératoire est caractérisée par une augmentation du catabolisme protéique, proportionnel à la gravité de l'intervention et aux éventuelles complications postopératoires, mais qui dépend également de l'état nutritionnel préopératoire, de l'âge et du sexe. Le rôle du catabolisme protéique est important pour la cicatrisation et la dépression des moyens de défense immunitaire. Pour synthétiser, la réaction au stress chirurgical est le résultat d'interactions complexes entre les systèmes nerveux, endocriniens et immunitaires.

L'ensemble des éléments propres au protocole de RAC, qu'ils soient génériques ou propres à une discipline spécifique, visent tous le même objectif : maintenir l'homéostasie entre les composantes susmentionnées, pour minimiser les effets de la phase catabolique et améliorer la réponse au stress induit par l'intervention.

A titre d'exemple, la réduction de la résistance à l'insuline favorise une fonction cellulaire adéquate au cours d'une blessure, que l'on peut apparenter au traumatisme chirurgical. La série d'éléments suivants contribue à cet objectif: un accompagnement nutritionnel préopératoire pour les patients dénutris, charge en glucides avant la chirurgie pour minimiser résistance à l'insuline postopératoire, analgésie péridurale ou rachidienne réduire la réponse au stress endocrinien, des anti-inflammatoires pour réduire la réponse inflammatoire, une alimentation précoce après chirurgie pour un apport énergétique adéquat et un contrôle optimal de la douleur pour minimiser le stress et résistance à l'insuline.

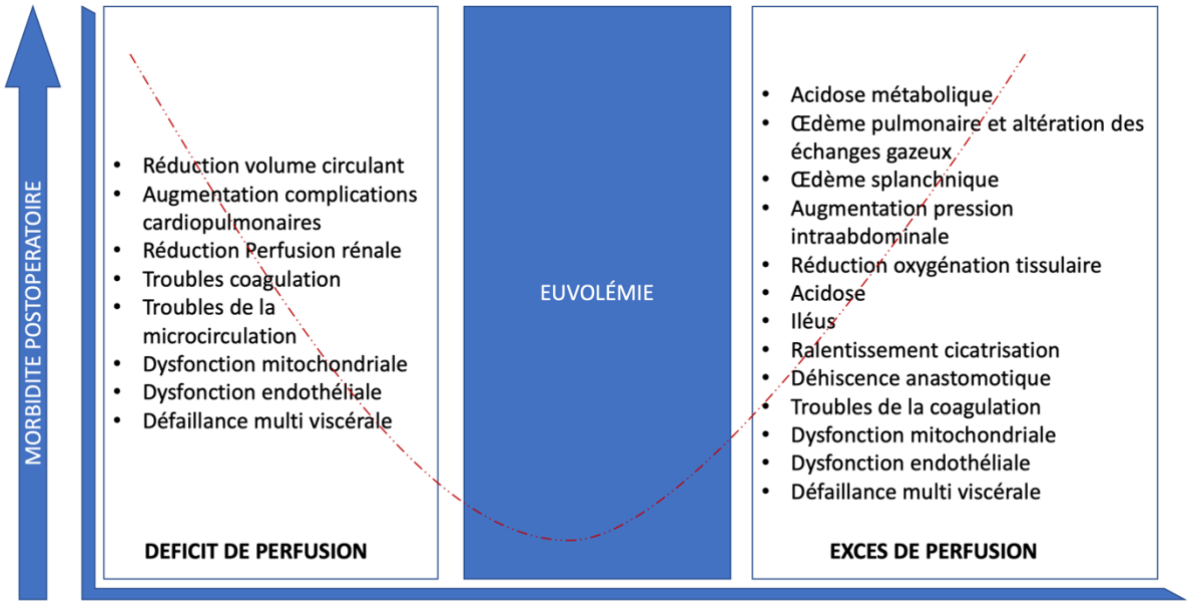


Figure 3 *La courbe dose-réponse pour le remplissage vasculaire et les effets du déséquilibre. Adapté de Basic Concepts of Fluid and Electrolyte Therapy*[22]*.*

Les programmes de RAC visent également à minimiser les changements de fluides. Trop peu de volume circulant peut entraîner une baisse de la perfusion tissulaire ainsi qu'une dysfonction d'organe, alors que le sel intraveineux et la surcharge liquidienne est reconnue comme une cause majeure d'iléus postopératoire et de complications cardiovasculaires.

2.3.3.1 SOINS PLURIDISCIPLINAIRES

Le remplacement des approches traditionnelles de soins chirurgicaux par des pratiques fondées sur l'évidence a mis en évidence comment la récupération puisse être améliorée et la durée de convalescence diminuée[3]. Les domaines d'application comprennent l'anesthésie et réanimation, l'analgésie, la réduction du stress chirurgical, la gestion des fluides, la chirurgie invasive minimale, la nutrition et la déambulation précoce.

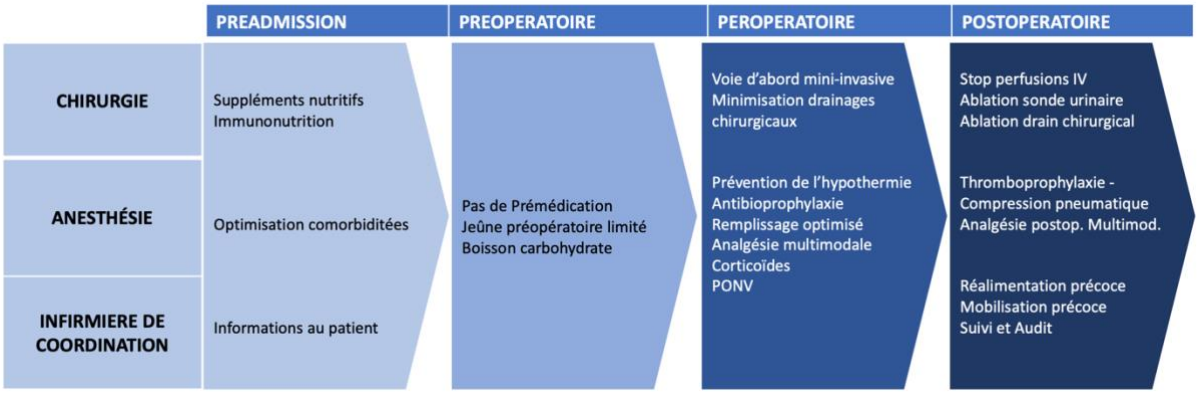


Figure 4 *Aperçu d'un organigramme indiquant les différentes phases d'un protocole RAC générique, avec les rôles de chaque professionnel de santé impliqué pendant les des différentes phases du parcours de soins. PONV : Nausées et vomissements post-opératoires; IV intraveineux. Adapté de Ljungqvist et al[3].*

Aucun élément à lui seul permet l'amélioration des résultats après chirurgie, et l'approche des soins périopératoires doit être multimodale pour stimuler la récupération. La clé est de rechercher la synergie entre un élément du processus et le suivant. Puisque les éléments de la RAC sont mis en œuvre par différents acteurs de soins tout le long du parcours de soins, travaillant dans différents services, une approche multidisciplinaire et multimodale est nécessaire. Cette approche incorpore non seulement chirurgiens et anesthésistes, mais également des infirmières, aides-soignants, diététiciens et kinésithérapeutes en tant que participants actifs de l'équipe de soins.

2.3.3.2 La TEAM RAC

Les théories behaviouristes (ou comportementalistes) suggèrent que pour qu'un individu puisse changer d'attitude, il doit y avoir un avantage ou une récompense à la clé. L'adhésion et la motivation personnelle envers un concept sont bien plus importantes que les directives « verticales » d'un(e) chef de service, de département ou directeur d'hôpital. Cependant, la participation des directions est importante pour le changement, car ils peuvent fournir des informations, des ressources, du soutien et des encouragements. La première étape pour que l'adhésion se produise est que l'individu éprouve une insatisfaction ou un mécontentement à l'égard du système actuel et qu'il soit donc motivé à faire quelque chose de différent. C'est le contraire de ceux qui veulent maintenir le *statu quo*[23].

Voilà pourquoi le cœur du changement des pratique doit reposer sur une équipe de personnes « clés » (ou « champions ») au sein des unités concernées, véritables moteurs du changement. La leadership médicale est le plus souvent portée par un chirurgien, épaulé par un anesthésiste, même si cette configuration n'est pas du tout exclusive. Pour une implémentation efficace et réussie, la cohérence entre les champions est capitale[24]. La coordination est généralement confiée à un membre de l'équipe paramédicale (en Europe souvent un(e) infirmièr(e)) de coordination ou, aux États-Unis, un médecin assistant), qui remplit un rôle clé en tant que «moteur» de l'équipe ERAS. Grace à du temps dédié à la gestion des questions pratiques, il/elle peut rédiger et distribuer de la documentation spécifique comme des mémos et des instructions pour les malades, réaliser des retours d'information aux unités d'hospitalisation, ainsi qu'organiser la formation continue du nouveau personnel. La personne occupant ce rôle est bien placée pour gérer le processus d'audit, et saisir la base de données prospective. La participation des autres disciplines, comme les diététiciens, ergothérapeutes ou kinésithérapeutes sont essentielles pour des résultats de haut niveau.

2.3.3.3 LE PARCOURS DU PATIENT

Un défi fondamental dans la prise en charge du patient chirurgical réside dans les différentes phases du parcours de soins et de l'hospitalisation que le malade traverse : consultations, unités préopératoires, salle d'opération, salle de réveil, réanimation, et le service d'hospitalisation conventionnelle.

Le personnel hospitalier se concentre souvent sur la gestion des situation cliniques avec peu de possibilités de réflexion stratégique, en amont ou en aval.

Chaque unité a son propre objectif, avec du personnel soignant (médical et non médical) souvent dédié. Peu d'acteurs de soins, lors d'une prise en charge chirurgicale, ont la possibilité de voir un patient à travers toutes les étapes de l'hospitalisation (et d'avoir ainsi conscience de la vision d'ensemble, « *the bigger picture* »).

Il y a une vingtaine d'éléments principaux du protocole de soins RAC, qui reposent sur des solides bases scientifiques[3]. Ces éléments sont appliqués tout le long du parcours du patient, et dispensés par différents services et professionnels au sein de l'hôpital, ce qui explique pourquoi le chirurgien, en tant que clinicien ayant la responsabilité globale du patient, ait la meilleure opportunité d'avoir une vue d'ensemble, pour guider le processus.

La reproductibilité de ce parcours présuppose un accord solide sur des objectifs consensuels, comme par exemple des critères définissant la sortie des malades. La définition de récupération fonctionnelle, terme général utilisé pour rendre compte des processus qui aboutissent à la restitution partielle ou complète du fonctionnement d'un organe atteint par une lésion (comme une intervention chirurgicale), est particulièrement utile. Cette dernière en chirurgie a été définie par une liste de critères[25,26] : reprise d'une alimentation per os, transit, la douleur est contrôlée par des analgésiques oraux, il ou elle est capable de se mobiliser suffisamment pour les soins personnels, et il n'y a pas de complications nécessitant soins hospitaliers[3]. Lorsque l'ensemble de ces critères sont remplis, alors le patient a récupéré suffisamment pour que la sortie soit justifié d'un point de vue médical[27]. La standardisation des critères de sortie permet leur reproductibilité, harmonisant ainsi leur mesure.

2.3.3.4 RECOMMENDATIONS BASEES SUR LA LITERATURE

La formation chirurgicale est traditionnellement basée sur un système de compagnonnage, avec des enseignants qui transmettent leurs techniques opératoires et méthodes de soins périopératoires aux étudiants (internes et chef de clinique). Ces approches étaient généralement acceptées et efficaces selon les critères traditionnelles, et les chirurgiens reproduisaient à leur tour, plus ou moins fidèlement, ces méthodes de soins tout au long de leur vie professionnelle[28]. Cependant, des études rigoureuses portant sur les soins périopératoires ont mis en évidence comment de nombreuses approches traditionnelles telles que la préparation intestinale[29,30], l'utilisation de sondes nasogastriques[31] ou des drains chirurgicaux[32,33], le jeune[34] ou l'alitement prolongé[35,36] sont inutiles, voir même nuisibles[31,37,38].

Après les premières publications de H. Kehlet[4,16,38] des société savantes (ERAS et GRACE-ASSO) ont regroupé et mis à jour les données les plus récentes sur les soins peropératoires, permettant de publier un premier document consensuel pour la chirurgie colique[5] et quelques année plus tard sur la chirurgie colorectale[39,40]. Par la suite, nombreuses recommandations ont suivi en cardiaque[41], orthopédique[42], chirurgie pancréatique[43,44], chirurgie gynécologique majeure[45], bariatrique[46], œsophagienne[47],chirurgie de la carcinose péritonéale[48] ou hépatique[7]. Pour certaines d'entre elles, des mises à jour ont déjà été publiées[44,49] (notamment, la mise à jour des recommandations en chirurgie hépatique est actuellement en cours). Cette dernière est le domaine chirurgical qui se rapproche le plus de la transplantation hépatique.

Une controverse actuelle dans le domaine de la récupération améliorée concerne le nombre d'éléments individuels qui doivent être inclus dans un protocole RAC. L'inclusion de plusieurs éléments (vingt au minimum) est critiquée comme étant trop complexe, et certains auteurs affirment que seuls 5 à 7 soient nécessaires[50]. L'approche scientifique de la RAC consiste en revanche à inclure tous les éléments qui améliorent les résultats, au lieu d'essayer de définir un nombre minimum d'éléments[13]. De plus, certains éléments sont susceptibles d'évoluer dans le temps. Il incombe alors à chaque équipe d'appliquer autant d'éléments que possible, ce qui à son tour se traduit par de meilleurs résultats. Les données disponibles suggèrent une forte relation dose-réponse entre une adhésion élevée au protocole et une amélioration des résultats[51], avec un seuil de « haute adhérence » allant de 60 % à 90 % en chirurgie colorectale[51–54] et de 67 % à 74% en chirurgie hépatobiliaire[55–57].

2.3.3.5 AUDIT

Les professionnels de la santé, et les chirurgiens en particulier, ont tendance à surestimer les résultats de leur prise en charge, notamment en termes de durée séjour « perçue » et réelle. Enfin, certaines équipes chirurgicales estiment adhérer aux principes de la RAC alors qu'en fait, ils ne les utilisent qu'en partie. Pour permettre une visualisation objective de l'adhésion au protocole, basées sur des données concrètes, l'équipe de soins est supportée par un système d'audit interactif.

Ce dernier, digitalisé et géré par la coordination locale (infirmier/e, chirurgien ou anesthésiste) permet de suivre les résultats en temps réel tant à l'échelle du patient que globale de l'ensemble du service.

A présent, deux systèmes sont disponibles, propres à la société ERAS (http://www.erassociety.org) et GRACE-ASSO (https://www.grace-

audit.fr/accueil/index.php), avec des volets déclinés pour chaque spécialité. (colorectale, gynécologique, hépatique, pancréatique, etc.).

Les différents volets permettent de suivre la saisie progressive des dossiers de chaque malade. Les résultats et graphiques fournis par ce système d'audit interactif peuvent être utilisé lors des réunions d'implémentation et de surveillance.

2.3.3.6 IMPLEMENTATION D'UN PROGRAMME RAC

À ce propos, 310 millions d'opérations majeures sont effectuées chaque année. Les données suggèrent qu'un programme RAC puisse contribuer à réduire le taux de complications de 10% à 20%, en aidant les unités à adopter des soins fondés sur des données probantes[3].

La mise en œuvre de nouvelles pratiques – y compris la RAC – est difficile, et les nouveaux traitements sont lents à se diffuser en pratique courante. Pour que les programmes RAC réussissent, peu de place peut être laissée à l'improvisation, et les efforts pour implémenter correctement un tel programme ne doivent pas être sous-estimés[58].

La mise en œuvre d'un programme de RAC doit être systématique avec l'implication d'une équipe multidisciplinaire, et peut être facilitée par le soutien d'experts d'autres centres pour alléger la complexité du processus d'implémentation[13]. Un programme RAC réussi doit couvrir les principes fondés sur des preuves avec une formation axée sur l'équipe. Les éléments essentiels sont le recueil de données et le suivi des résultats à l'aide d'un système d'audit avec un examen complet lors de réunions multidisciplinaires régulières. L'objectif est de documenter dans quelle mesure les éléments sont utilisés (adhésion). Les équipes travaillent ensemble pour itérer vers une conformité accrue aux recommandations, ce qui se traduit par de meilleurs résultats cliniques.

Des réunions d'équipe régulières et nécessitant d'une participation assidue sont essentielles à l'implémentation d'un programme RAC. Au départ, le groupe devrait se réunir avec une cadence hebdomadaire, pour vérifier l'adhésion au protocole et mettre en œuvre les changements nécessaires pour améliorer les pratiques. Au fil du temps, la fréquence des réunions peut être réduite à une semaine sur deux, mais la participation aux réunions doit rester un engagement de la part de chaque membre de l'équipe.

2.3.3.7 DURABILITE DU PROGRAMME RAC

L'intégration d'une innovation efficace dans la routine quotidienne est, d'une manière générale, un processus dynamique et difficile, avec des résultats hétérogènes. De plus, une fois l'implémentation réussie, il y a souvent une tendance à retomber dans les anciennes habitudes après la fin de la mise en œuvre. Des recherches en santé publique montrent que jusqu'à 40% de toutes les innovations ne perdurent pas dès la fin de la phase d'implémentation et des financement initiaux[59]. Cela peut être considéré comme une perte de temps et d'argent. De plus, l'arrêt des innovations réussies pourrait se traduire par des soins moins performants pour les patients, pouvant induire de la frustration auprès du personnel soignant et diminuer le soutien aux futurs protocoles de recherche. Par conséquent, il est important que les avantages obtenus par une intervention efficace soient maintenus après leur mise en œuvre. Bien que la durabilité soit un sujet important dans le domaine de la santé, il n'y a pas de définition standard de la durabilité. Il peut être considéré comme « maintenir les gains » ou «maintenir les avantages en santé» et «poursuivre les activités du programme au sein d'une structure organisationnelle»[59,60]. La durabilité du changement existe lorsqu'une innovation nouvellement mise en œuvre continue de fournir les avantages obtenus sur une plus longue période de temps, ne revient pas aux processus habituels et surtout devient « la façon dont les choses sont faites ici » (ou la nouvelle routine), même après la fin du projet d'implémentation.

Les outils d'audit sont un moyen simple et performant pour mesurer l'adhérence au protocole de RAC et le rappeler régulièrement à l'ensemble des équipes.

Grace à ce système d'audit, il a été possible de mesurer la durabilité d'un programme RAC en chirurgie colorectale au sein de 10 hôpitaux néerlandais[61]. Lors de la phase d'implémentation une amélioration de la durée de séjour d'une médiane de 9 jours à 5,2 jours avait été observée, avec un taux d'adhérence au protocole de 75%. Après une période variable entre 3 et 5 ans du processus d'implémentation, la durée de séjour a été mesurée à 6 jours en médiane, avec un taux d'adhérence au protocole de 67%. Malgré une légère diminution de l'observance du protocole, le programme RAC s'est maintenu raisonnablement stable dans les 10 hôpitaux sélectionnés, bien qu'il y ait eu une certaine variation entre les hôpitaux. Notamment, la baisse du taux d'adhésion a été observée pour les items les plus « difficiles », comme l'arrêt des perfusions dès le premier jour postopératoire (de 36% à 9%), la mobilisation pendant plus de 3h (de 90% à 38%) et la reprise de l'alimentation per os (de 65% à 37%).

2.3.3.8 CRITERES DE JUGEMENT D'UN PROGRAMME RAC

Le but des programmes de RAC est d'améliorer la récupération post-opératoire, qui doit être par conséquent mesurée le plus objectivement possible à travers l'évaluation d'un ou de plusieurs indicateurs. Une révision de la littérature publiée en 2014[62] a fourni un cadre pour mesurer les résultats des programmes de récupération améliorée après la chirurgie. Cependant, comme il n'y a pas de définition unique de récupération, il existe des phases qui se chevauchent et dont le principal résultat d'intérêt peut varier en fonction de l'acteur (de soins) concerné : chirurgien, anesthésiste, infirmier de parcours, ou patient. Pendant la phase la plus précoce (de la fin de la chirurgie à la sortie de l'unité de soins post-anesthésiques), les résultats biologiques et physiologiques sont les critères de jugement les plus considérés. Dans la phase intermédiaire (de l'unité de soins intensifs à la sortie de l'hôpital), les symptômes liés à la douleur et à la fonction gastro-intestinale ainsi que les activités de base sont importants. Des études sur la RAC ont rapporté des résultats portant sur les complications, la durée du séjour à l'hôpital, la mobilisation et la fonction gastro-intestinale, principalement pendant l'hospitalisation. Néanmoins, les patients (résultats reportés par les patients, ou *Patient Reported Outcomes*, PRO) définissent la récupération comme un retour à un mode de fonctionnement normal, ce qui est un processus qui se déroule sur des semaines ou des mois (phase tardive). Les résultats sur l'état fonctionnel (par exemple, l'activité physique, les activités de la vie quotidienne) et la santé globale (par exemple, la qualité de vie) sont très importants dans cette phase. À ce jour, peu d'études rapportant l'efficacité de la RAC par rapport aux soins conventionnels ont inclus l'état fonctionnel ou la qualité de vie, et il existe peu d'informations sur la récupération après la sortie de l'hôpital.

Pour résumer, plusieurs indicateurs de récupération post-opératoires ont été utilisés, mais le plus répandu reste la réduction de la durée d'hospitalisation. Cependant, la durée d'hospitalisation qui dépend directement de la date de sortie du patient peut être influencée par des aspects logistiques externes retardant le retour du patient à domicile, comme par exemple l'absence d'un entourage familial ou de mesures d'aide à domicile optimaux, ou encore l'existence d'une incompatibilité entre la date théorique de sortie et la faisabilité organisationnelle d'une sortie de l'hôpital vers le domicile (pas de sortie le weekend, pas de médicaments disponibles à la pharmacie en ville etc…). De plus, même si les malades satisfont les critères médicaux de sortie, ils restent culturellement souvent anxieux par un retour à domicile trop précoce. D'autres critères cliniques d'évaluation de la RAC incluent la mortalité à trente jours, la nécessité d'une

réhospitalisation à trente jours et/ou la survenue de complications post-opératoires. Cependant, ils ne donnent qu'un aperçu des complications majeures ou des problèmes postopératoires chez les patients qui ont été réadmis ou traités[63].

A. Durée de séjour

La durée d'hospitalisation a été considérée pendant longtemps comme un marqueur indirect de récupération et de performance du système de soins[64]. Une métanalyse analysant l'impact de la RAC en chirurgie colorectale a mis en évidence une réduction de la DMS (MD -2.94 jours; 95% CI -3.69 to -2.19)[65]. Des résultats similaires ont été observés en chirurgie hépatobiliaire. Une étude récente cas-témoin européenne a comparé le parcours RAC versus standard en chirurgie hépatobiliaire chez 100 patients (n=50 RAC, n=50 contrôle) appariés sur l'étendue de la résection, la localisation tumorale et la voie chirurgicale ouverte/laparoscopique. Il a été observé dans le groupe RAC une réduction de 38% (2,5 jours) de la durée de séjour (4 jours groupe RAC vs 6.5 jours groupe contrôle, $p < 0.001$), en absence de différences significatives en terme de complications postopératoires ou de taux de réadmissions[66]. Sur la même ligne, une étude monocentrique a mis en évidence une réduction de la DMS à 2 jours après résection hépatique par laparoscopie et à 4-5 jours par laparotomie[67].

Les méta-analyses en chirurgie hépatique considérant ce type d'indicateur reportent une réduction de -2.07 à -3.31 jours en moyenne de la durée de séjour dans le groupe RAC[68–72].

B. Délai de récupération fonctionnelle

Plus que la durée d'hospitalisation, le délai entre une intervention et l'indication médicale de sortie (IMS) semble être un paramètre plus objectif s'affranchissant des contraintes logistiques variables selon les centres, répondant à des critères médicaux précis, permettant ainsi de « normer » ce délai et de comparer les durées d'hospitalisation entre différents centres ou pays. L'IMS est définie par une liste de critères (de sortie) consensuels, validés pour les programmes de RAC en chirurgie hépatobiliaire[26,67]: il est justifié, d'un point de vue médical, d'autoriser la sortie d'un patient (indication médicale de sortie) quand les critères de récupération fonctionnelle sont satisfaits.

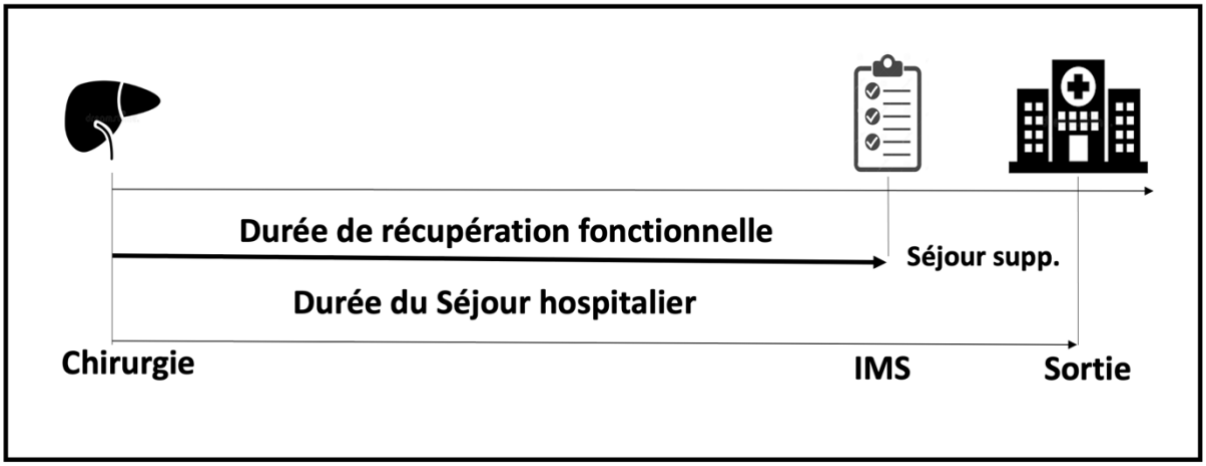


Figure 5 *Schéma du rapport entre la durée de récupération fonctionnelle (délai entre chirurgie et indication médicale de sortie) et durée de séjour hospitalier (délai entre chirurgie et sortie réelle). L'indication médicale de sortie (IMS) repose sur la satisfaction d'une liste de critères de récupération fonctionnelle.*

Le patient est considéré avoir atteint un bon niveau de récupération fonctionnelle, et être par conséquent capable de sortir d'hospitalisation. A présent, l'IMS n'a pour l'instant été définie que dans les protocoles de RAC.

C. Effet sur les complications à court terme et la mortalité précoce.

Une méta-analyse issue de la base Cochrane incluant des études randomisées et contrôlées en chirurgie colorectale a mis en évidence une réduction significative du risque de complications (RR 0.50; 95% CI 0.35 to 0.72), avec des taux similaires de réadmissions[65] lorsque le protocole RAC était appliqué. De plus, une étude sur plus de 900 patients atteints de cancer colorectal a mis en évidence qu'une adhésion >70% au protocole de RAC est corrélée à une réduction du taux de complications (OR = 0.69, P < 0.001), de réadmission (OR = 0.88, P < 0.001), mais aussi du taux de mortalité de 42%[52]. Dans ce dernier domaine, l'applicabilité de protocole de RAC semble sûre et faisable, avec un taux de réadmission de 6% et une mortalité nulle.

Trois méta-analyses[70–72] évaluant l'impact d'un protocole RAC en chirurgie hépatobiliaire portant respectivement sur 580, 723 et 2575 patients ont clairement mis en évidence une réduction significative du taux de complications (0.34<OR<0.66).

D. Effet sur les coûts hospitaliers

Les programmes de RAC sont souvent associés à une réduction des coûts financiers[73–75]. Cette économie a été montrée aussi bien à l'échelle locale qu'à l'échelle régionale, comme l'illustrent les deux exemples suivants :

- Une étude simulant la mise en place d'un programme RAC dans un centre tertiaire aux États-Unis a permis de mettre en évidence une économie dès la première année de 171% sur des coûts d'hospitalisation, et de 71% après déduction de l'investissement initial réalisé pour la formation et mise en place du protocole RAC[76].
- Au Canada, le service de santé publique a soutenu les Sociétés ERAS afin de démocratiser l'implantation de tels programmes en chirurgie colorectale. Les premiers résultats sont très prometteurs avec une diminution de 8% des réadmissions et du séjour pour les patients hospitalisés, avec une économie variant de $2800 to $5900 par patient[77].

Plusieurs revues de la littérature ont en revanche souligné que le nombre d'études randomisées contrôlées s'intéressant aux données économiques était faible, et que ces études comportaient de nombreux biais méthodologiques. Ces écueils rendent nécessaires la réalisation d'autres études randomisées contrôlées de méthodologie solide, centrées sur le rapport coûts-efficacités de la mise en place des programmes ERAS/RAC[78,79].

E. Résultats à long terme de la RAC.

Les avantages à long terme d'une récupération rapide à l'aide de la RAC sont moins bien connus[80], avec des résultats qui commencent à être publiés. Un rapport sur plus de 900 patients atteints d'un cancer colorectal a montré que, avec un taux d'adhérence supérieur à 70% des items du protocole RAC, la mortalité a baissé de 42% par rapport aux patients avec un taux d'adhérence inférieur à 70%[51]. Dans cette étude les données suggèrent une association plutôt qu'un lien de causalité, et d'autres variables peuvent avoir contribué directement ou indirectement à ce résultat. Par exemple, le groupe avec une observance plus élevée a présenté un moindre taux de complications, ce qui peut avoir affecté les résultats observés. En effet, le lien entre complications postopératoires et résultats oncologiques médiocres ont été largement mis en évidence[81–83], ainsi que le fait que les complications chirurgicales peuvent retarder le début de la chimiothérapie postopératoire. Une étude monocentrique Suisse suggère que une haute compliance à la RAC semble être associée à une réduction du délai avant la chimiothérapie adjuvante, chez des jeunes patients atteints de tumeurs malignes hépatobiliaires et pancréatiques[55].

Une étude américaine[84] « avant-après » l'implémentation d'un programme RAC, incluant près de 9500 patients ayant subi une chirurgie orthopédique majeure, mais aussi hépatobiliaire, colorectale, gynécologique, bariatrique ou urologique, a observé que la mortalité à 30 jours a diminuée de 0,6 % avant RAC à 0,2 % après

RAC (p = 0.002). De même, la mortalité à 1 et 2 ans après chirurgie est passée de 5,1% et 9% avant implémentation à 3,9 % et 6.2% après implémentation, respectivement. Les bénéfices initiaux des programmes de RAC sont étendus à des domaines de la chirurgie de plus en plus complexes. Probablement la phase où les seuls résultats de la RAC se focalisaient sur faisabilité, durée de séjour et complications est terminée[85,86]. Sur la base des études susmentionnés, la RAC peut être associée à une réduction de la mortalité postopératoire.

2.3.3.9 LE FUTUR DE LA RAC

Les principes de la RAC sont appliqués à la plupart des spécialités chirurgicales, et l'innovation en cours doit continuer à permettre aux processus de s'améliorer. Il y a un intérêt croissant sur des items propres à certaines disciplines, pour essayer d'améliorer les résultats.

L'étape suivante de la RAC est de pouvoir produire rapidement de la recherche de qualité à couts réduits[13].

Cela peut être possible car le système (GRACE ou ERAS) fournit les bases à la fois pour des essais prospectifs et de la recherche sur registre, avec un grand nombre de patients avec une prise en charge « homogène », par le biais du même parcours de soins. Proposer un changement du protocole en une seule étape et d'en analyser l'impact en cascade prospectivement sur l'ensemble des centres participants, peut représenter une manière complémentaire d'étudier de nouvelles interventions plutôt que de s'appuyer sur des couteux essais cliniques[3].

2.3.3.10 CONCLUSION

Les programmes de récupération améliorée après chirurgie représentent une innovation et un changement de paradigme dans la façon dont les soins chirurgicaux sont dispensés, tout au long du parcours de soins. Ces résultats reposent sur une nouvelle approche du travail d'équipe, grâce à un audit continu et au changement basé sur l'évidence médicale académique. La RAC après chirurgie est associée à des avantages sur les résultats à court et à long terme pour les patients, tout en améliorant la qualité et l'organisation des soins et tout en permettant des économies de santé.

2.4 LA TRANSPLANTATION HEPATIQUE

La greffe ou transplantation hépatique (TH) représente à ce jour le traitement de référence de patients atteints d'une insuffisance hépatique terminale ou de carcinome hépatocellulaire (CHC).
Depuis son introduction en 1967 aux États-Unis et en 1968 en Europe (Sir Roy Calne au Royaume Uni et par les professeurs Garnier et Clot en France), la TH a évolué rapidement, avec plus de 80 000 procédures réalisées en Europe à ce jour[2]. Les taux de survie se sont considérablement améliorés au cours des 25 dernières années, atteignant des taux de 79 à 87% à 1 an et de 66 à 87% à 5 ans, respectivement[87–90].

Ce succès repose en grande partie sur plusieurs avancées comme l'introduction de nouveaux agents immunosuppresseurs et de solutions de préservation de greffons[91], l'amélioration des techniques chirurgicales, le diagnostic précoce et la prise en charge des complications après TH[92]. Sur le long terme, au-delà de la récidive de la maladie initiale, le suivi se focalise sur les effets secondaires directs et indirects du traitement immunosuppresseur.
En 2019, 1356 greffes hépatiques ont été réalisées en France, soit une hausse de 2,3% (+31 greffes) par rapport à l'année précédente[93].

Pendant les dernières années et de manière constante, une extension des indications de TH a été observée, avec comme corollaire une augmentation des inscriptions sur liste d'attente de greffe. A titre d'exemple, en France, 3 400 candidats étaient inscrits sur liste en 2019[93], avec un taux de croissance constant : 2,8% en 1 an, 11,3% en 4 ans et une croissance globale de 59,2% en 10 ans.

En revanche, la pénurie de greffons est un problème constant, en dehors de quelques exceptions comme les pays Scandinaves ou l'Espagne. Selon le rapport de l'Agence de la Biomédecine, en France en 2019, l'évolution de la pénurie peut être mesurée par 2 indicateurs[93] :

- le nombre de <u>nouveaux inscrits</u> pour un greffon (1,4 inscrits pour un greffon),
- le nombre <u>receveurs actifs</u> sur liste d'attente pour un greffon (2 receveurs pour un greffon).

L'inadéquation entre la demande et l'offre de greffons se traduit par l'augmentation de la durée d'attente, avec comme effet conséquence une augmentation du risque de décéder ou sortir de liste (pour aggravation), en hausse constante depuis 2006. Parmi

les candidats à la greffe, on note aussi une aggravation de leur condition générale en rapport avec l'hépatopatie sous-jacente ou les comorbidités associées.

Le moment de la transplantation est crucial : après l'apparition de complications systémiques la greffe serait futile, alors que l'avantage d'une greffe trop précoce pourrait être déséquilibré par le risque chirurgical excessif et les complications d'une immunosuppression à vie.

2.4.1 INDICATIONS

Les principales indications de la TH en Europe sont résumés dans le rapport du registre européen de la transplantation hépatique (*European Liver Transplant Registry* - ELTR) de 2018[94].

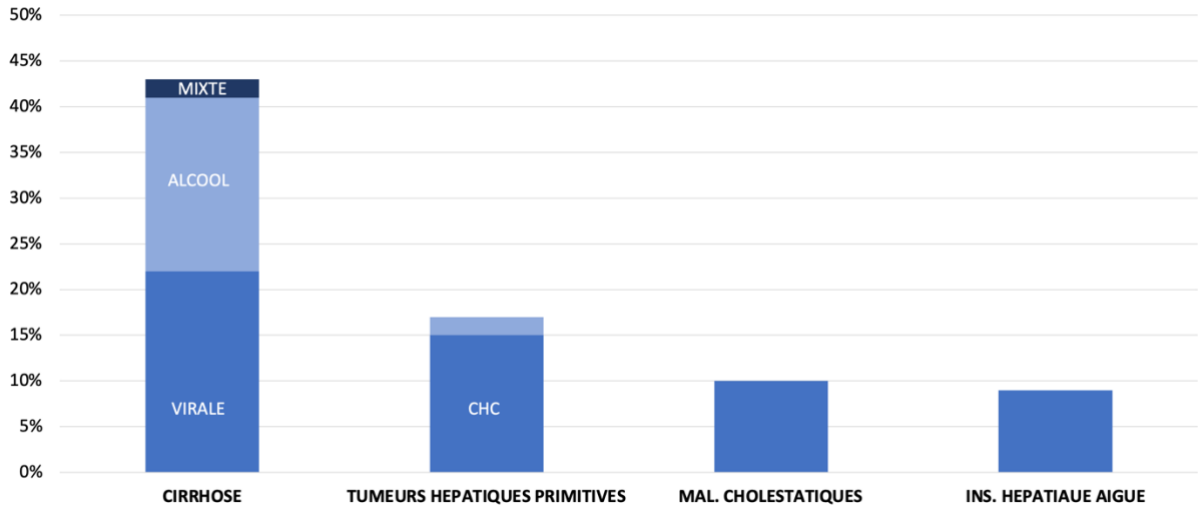


***Figure 6**. Histogramme des principales indications de greffe. Données source extraites du rapport de l'ELTR de 2018[94].*

Pour les adultes, la cirrhose était l'indication la plus fréquente (50%), principalement post-virale (22%, dont 12% par le virus de l'hépatite C-VHC et 5% par le virus de l'hépatite B-VHB), ou due à l'abus d'alcool (19%). Les cirrhoses combinées virales et alcooliques (OH) représentaient 2,4 % des indications, majoritairement VHC-OH (2%).

La cirrhose est suivie de trois indications majeures :

- les tumeurs hépatiques primitives (17%, à prédominance de carcinome hépatocellulaire – CHC, 15%).
- les maladies cholestatiques (10%).

- l'insuffisance hépatique aiguë (9,1%, dont 2% d'origine virale, 2,4% médicamenteuse, 0,3% toxique non médicamenteuse et 4,4% de cause inconnue).

Les étiologies les plus courantes de la cirrhose sous-jacente chez les patients atteints de CHC étaient le VHC (43%), l'abus d'alcool (27%) et le VHB (16%).

Les maladies cholestatiques comprenaient la cirrhose biliaire primitive (5%) et la cholangite sclérosante primitive (5%). Les maladies métaboliques représentaient 6 % de toutes les indications, les trois principales indications étant la polyneuropathie amyloïde familiale, la maladie de Wilson et le déficit en alpha-1-antitrypsine (1% chacune). Le syndrome de Budd-Chiari et les maladies hépatiques bénignes (principalement maladie polykystique) ne représentaient que l'1% des indications de la TH. Les tumeurs hépatiques secondaires (principalement neuroendocrines) représentaient 0,5% des TH.

2.4.2 BILAN PRE-TRANSPLANTATION

Chaque candidat potentiel à la greffe doit entreprendre un bilan extensif avant l'inscription sur liste d'attente. Le temps imprévisible passé sur la liste d'attente, le déclin progressif de la condition physique et des activités de la vie quotidienne, ainsi que le passage à la nouvelle condition « chronique » après TH nécessitant des traitements à vie sont des sources bien connues d'anxiété, de stress et de dépression chez les patients en liste d'attente[95–98]. De plus, une connaissance insuffisante de la maladie ou de la transplantation semble être associée à une moindre observance thérapeutique[99]. Les tendances actuelles en matière d'éducation des patients en chirurgie[100] suggèrent de programmer une éducation thérapeutique préopératoire précoce, avec répétition de messages éducatifs portant sur la période postopératoire et la prise en charge après la sortie. Dans une étude englobant un échantillon de patients sur liste d'attente de TH avec leurs familles[101], la période postopératoire représentait celle avec un besoin d'informations plus important que les périodes pré et peropératoires.

Les stratégies éducatives multidisciplinaires devraient impliquer un chirurgien, un anesthésiste-réanimateur et surtout un(e) infirmièr(e) ou un professionnel paramédical, comme lien entre le patient et l'équipe, instaurant des attitudes de confiance et permettant l'échange d'informations supplémentaires[98,100].

Age

En fonction des pays, la limite supérieure d'âge peut varier entre 60 et 70 ans, même si au-delà de 65 ans des évaluations cardiovasculaire, respiratoires ou neurologiques supplémentaires sont souvent indispensables pour formaliser la stratification du risque. La TH a déjà été réalisée chez des patients âgés de plus de 70 ans, même s'ils présentent un risque supplémentaire de complications cardiovasculaires[102]. Le taux de greffes hépatiques chez des patients âgés de plus de 65 ans est progressivement à la hausse, avec des résultats comparables à des candidats plus jeunes. Cette tendance est probablement liée au changement démographique impliquant une société sénescente, mais également au changement de l'épidémiologie des maladies hépatiques. Certaines équipes considèrent l'âge physiologique comme plus important que l'âge chronologique[103,104]. La décision finale d'inscrire sur liste un patient de 65–70 ans ou plus devrait reposer sur une discussion pluridisciplinaire prenant en compte non seulement l'hépatopathie sous-jacente, mais également l'ensemble des réserves physiologiques du patient. En effet, la baisse progressive de l'activité physique chez les patients cirrhotiques est un contributeur primaire à la fragilité, qui est associée à un risque majeur de décès sur liste d'attente, de taux d'infection postopératoire et de décès précoce après transplantation hépatique. L'analyse de la cohorte de l'étude longitudinale FrAILT[105] à San Francisco a permis aux chercheurs d'observer comment s'habiller était la première activité de la vie quotidienne pour laquelle les patients signalaient des difficultés, suivi de la toilette, du ménage et de la lessive, entre autres. Dans l'ensemble, ils ont observé comment la difficulté pour chaque activité de la vie quotidienne était associée à une augmentation de 60% du risque de décès sur liste d'attente.

Bilan de la fonction cardiovasculaire

Les malades atteints de cirrhose présentent souvent un débit cardiaque augmenté. De plus, une dysfonction cardiaque latente associant une altération de l'inotropisme avec dysfonction systolo-diatolique, ainsi que des anomalies électrophysiologiques, est souvent observée. Ce syndrome est connu sous le nom de cardiomyopathie cirrhotique[106]. Malgré la place cruciale de l'évaluation cardiaque dans le bilan pré-greffe, les modalités de sa réalisation restent débattues ; il n'existe aucun *gold-standard*. Les facteurs de risque cardiovasculaires sont associés à la maladie coronarienne chez les patients cirrhotiques ; ils devraient donc être explorés comme indicateurs du risque coronarien[107]. L'Électrocardiogramme et l'échographie cardiaque trans-thoracique devraient être proposés à chaque patient candidat à une greffe hépatique, dans l'objectif de dépister une maladie cardiaque sous-jacente. Dans le cas

de patients avec multiples facteurs de risques cardiovasculaires et âgés de plus de 50 ans, un test d'effort devrait être réalisé pour démasquer une ischémie myocardique asymptomatique. La capacité aerobique est sévèrement réduite chez une grande partie de patients avec hépatopathie chronique. Chez des malades en attente de greffe, le seuil anaérobique mesuré pendant l'exercice cardiopulmonaire est corrélé à la durée d'hospitalisation et à la survie postopératoire[108]

Bilan de la fonction respiratoire

Pour évaluer la fonction respiratoire, des tests fonctionnels pulmonaires et des imageries pulmonaires sont recommandées chez tous les patients candidats à la greffe de foie. Le syndrome hépato-pulmonaire (SHP) et l'hypertension porto-pulmonaire (HPP) sont deux complications pulmonaires fréquentes de la maladie hépatique.

Lorsque le SHP ou une HPP sont suspectées, des investigations complémentaires doivent être effectuées[109].

Le SHP est présent chez 10 à 17 % des patients cirrhotiques et se caractérise par des dilatations vasculaires intrapulmonaires, en particulier dans les régions basales du poumon. Il en résulte une hypoxémie, et une oxygénothérapie peut être nécessaire. La TH est le seul traitement efficace du SHP permettant de corriger l'hypoxémie, les échanges gazeux et de diminuer le shunt intrapulmonaire dans la plupart des cas. Le SHP peut être diagnostiqué en calculant le gradient d'oxygène alvéolo-artériel et en effectuant une échocardiographie de contraste[110]. La gravité du SHP n'est pas liée à la gravité de la maladie du foie et représente à elle seule une indication à la TH. Il est important de bien évaluer la gravité du SHP, puisque les patients avec une $PaO_2 < 50$ mmHg et aucune réversibilité à l'oxygène à 100 % peuvent présenter un risque d'insuffisance respiratoire irréversible pendant la période post-greffe et un risque élevé de mortalité périopératoire[111]. Il ne faut pas oublier non plus que chez la plupart des patients atteints de SHP, il existe une détérioration de la fonction respiratoire pendant les premiers jours après la greffe en raison de l'intervention chirurgicale elle-même. L'amélioration et la réversibilité du SHP peuvent prendre plusieurs mois[112].

L'HPP survient chez 2 à 8 % des patients cirrhotiques. Le diagnostic est suspecté lorsque la pression systolique artérielle pulmonaire est supérieure à 30 mmHg à l'échocardiographie et doit être confirmé par un cathétérisme cardiaque droit. L'HPP modérée (pression artérielle pulmonaire moyenne [PAPm]>35mmHg) et sévère (PAPm >45 mmHg) sont associées à une augmentation de la mortalité après LT, et représentent une contre-indication à la TH. Dans certains cas il est possible de

diminuer la pression artérielle pulmonaire par les dérivés de la prostacycline permettant d'effectuer dans un second temps une transplantation hépatique dans de bonnes conditions de sécurité. L'évolution de l'HPP après transplantation hépatique est souvent imprévisible notamment chez les patients ayant requis un traitement pharmacologique de l'hypertension artérielle pulmonaire avant transplantation hépatique. Il convient de surveiller ces patients de manière rapprochée en période péri-opératoire afin d'ajuster les traitements. Avec une expertise médico-chirurgicale, anesthésique et réanimatoire conséquente, les patients atteints d'HPP peuvent finalement être considérés pour la TH[113].

Bilan de la fonction rénale

Les patients cirrhotiques atteints d'insuffisance rénale ont un risque 7 fois plus élevée de décès, avec 50 % des patients décédés à 30 jours[114], par conséquent, l'évaluation de la fonction rénale est essentielle lors de l'évaluation d'un candidat à la greffe hépatique. Le syndrome hépatorénal, généralement réversible, doit être différencié d'autres causes d'insuffisance rénale aiguë, telles que le sepsis, l'hypovolémie et les autres causes d'atteinte rénale parenchymateuse. L'insuffisance rénale chronique est définie comme un taux de filtration glomérulaire (DFG) à <60 mL/min[115], depuis plus de trois mois.

Les patients atteints d'une cirrhose et présentant un DFG inférieur à 30 mL/min, un syndrome hépatorénal nécessitant une dialyse depuis plus de 8 - 12 semaines ou une fibrose de plus de 30% à la biopsie rénale, pourraient bénéficier d'une greffe combinée foie-rein[116]. L'indication d'une greffe combinée chez des malades avec une clearance entre 30 et 60 mL/min doit être retenue en fonction du risque de détérioration de la fonction rénale après TH, de nephrotoxicité des immunosuppresseurs, et de la pénurie de greffons rénaux.

Bilan complémentaire en vue d'une recherche de cancer

En dehors des tumeurs hépatiques représentant *per se* une indication à la transplantation (CHC, Cholangiocarcinome du hile), un antécédent de cancer déjà traité ne doit pas représenter une contre-indication absolue à la TH. Par conséquent, la survie et le risque de récidive à 1, 5 et 10 ans sous un traitement immunosuppresseur à long terme le traitement doit être estimé, au cas par cas, avec l'équipe d'oncologie. La pratique courante (qui peut être modulable en fonction des

pays et des instances locales) consiste à considérer une inscription sur liste si le risque de récidive est estimé à moins de 10%. De plus, généralement un intervalle de 5 ans sans récidive est souvent nécessaire pour exclure une récidive potentielle, mais cela peut varient considérablement selon le type de malignité. Cependant, à ce jour aucune donnée consistante n'a été publiée sur la prise en charge des patients candidats à la greffe et ayant un antécédent malignité extra hépatique.

Le dépistage des lésions tumorales doit toujours être effectuée lors du bilan pré-greffe en tenant compte des facteurs de risque tels que l'âge, le genre, la consommation d'alcool et le tabagisme. Le dépistage du cancer colorectal est obligatoire pour les candidats de plus de 50 ans. La recherche de cancer pulmonaire, des voies aérodigestives supérieurs (VADS), de l'œsophage et de la vessie est obligatoire dans cas de dépendance à l'alcool et au tabac.

Un dépistage spécifique de localisations secondaires dans le cadre de malignité hépatique doit se baser sur un scanner osseux et thoracique. Récemment, la tomographie par émission de positons (PET)-scan tend à être de plus en plus inclus en raison de sa sensibilité de dépistage de lésions néoplasiques non détectées pas l'imagerie standard[117].

Bilan nutritionnel

La cirrhose est associée à une dénutrition, et une carence protidique est présente chez près de 70% des patients atteints d'hépatopathie terminale[118–122]. Le déclin progressif de la capacité fonctionnelle associé à l'inactivité physique sont les principaux facteurs de fragilité[123,124], associés à leur tour à un risque majeur de décès sur liste d'attente, d'infection postopératoire et de décès précoce après transplantation[118,120,123,125].

Les paramètres cliniques et biologiques classiquement utilisés pour rechercher une malnutrition (IMC, préalbumine, etc.) peuvent ne pas s'appliquer en cas d'insuffisance hépatique sévère. Plusieurs auteurs ont récemment souligné le rôle de la sarcopénie (perte quantitative de masse musculaire, et qualitative par diminution de la force musculaire) évalué par la mesure de la surface du psoas au niveau de L3, sur la morbidité et la mortalité post-greffe[120,121,126]. A noter que même les malades obèses peuvent être atteint de sarcopénie : on parle alors d'obésité sarcopénique. Comme alternative, le test de marche de 6 minutes ou des scores dédiés[124] ont également été proposés afin de mieux capturer le profil de « fragilité » en pré-greffe hépatique[125].

Des interventions nutritionnelles avant la transplantation peuvent jouer un rôle important, et les recommandations de l'ESPEN (*European Society for Clinical Nutrition and Metabolism*)[121] suggèrent chez les malades cirrhotiques avec ou sans sarcopénie doivent avoir des régimes apportant 30-35 kcal x kg^{-1} x d^{-1} et 1,5g de protéines x kg^{-1} x d^{-1}. De même, il est proposé de minimiser les périodes de jeune en consommant trois à cinq repas par jour et une collation en fin de soirée pour améliorer et maintenir le capital protéique[121].

En dehors de rares cas de TH réalisée à partir d'un donneur vivant, où la greffe peut être « programmée », la plupart des transplantations dans les pays occidentaux sont majoritairement issues de donneurs décédés (DCD). En d'autres termes, le caractère imprévisible de la greffe implique l'absence de toute planification préopératoire à court terme, notamment en termes d'optimisation nutritionnelle[127].

2.4.3 TYPE DE DONNEURS ET GREFFONS

Chaque pays est libre d'organiser le système de transplantation hépatique en utilisant des greffons issus de donneurs décédés (mort cérébrale ou après arrêt cardiaque) et/ou de donneurs vivants.

Transplantation hépatique conventionnelle ou ''standard'', avec greffon entier

Le greffon est implanté dans le quadrant abdominal supérieur droit, en position orthotopique, en lieu et place du foie natif. La technique chirurgicale diffère en fonction de la conservation ou du remplacement de la veine cave inférieure (VCI). Selon une enquête portant sur plus de 90 programmes de transplantation en Europe et aux États Unis, la préservation de la VCI native est utilisée dans plus de 90% des cas[128]. Lorsque la VCI ne peut pas être conservée pour des raisons techniques (volumineux segment I, polikystose) ou oncologiques (CHC au contact de la VCI), un remplacement par la VCI du greffon sera réalisé avec deux anastomoses termino-terminales *supra* et *infra* hépatiques. L'anastomose entre la VCI du greffon et du receveur est suivie de l'anastomose porte, artérielle et biliaire[128].

Le succès de la TH a entraîné une inadéquation entre le nombre de malades inscrits en liste et les greffons disponibles : l'augmentation du taux de sortie de liste (*drop out*) pour morbidité et mortalité a conduit à la recherche d'alternatives pour élargir le pool de greffons.

Transplantation hépatique par greffon partagé

Au cours des 20 dernières années, les listes d'attente en chirurgie pédiatrique ont été réduites avec succès grâce à l'introduction de la TH segmentaire, y compris le greffon réduit, le split et le donneur vivant[129–131].

Aujourd'hui le split peut être considéré comme une alternative non inférieure à un greffon entier, en termes de survie du patient et du greffon, sur la base des séries recentes[131–134].

Dans les pays asiatiques, où les taux de TH avec des greffons décédés est négligeable[135] l'utilisation du donneur vivant s'est progressivement étendue, culminant avec la même procédure sur des patients adultes recevant des greffes de foie gauche ou droit par donneur vivant. L'introduction de l'abord mini-invasif a contribué à une relative diffusion de la procédure[136,137]. Cependant, bien que la greffe par donneur vivant ait été fortement stimulé dans les pays asiatiques, aux États-Unis et en Europe occidentale, la pratique est encore limitée, à peine dépassant 6% du nombre de greffes[138].

Cependant, ces techniques n'ont que marginalement augmenté le pool d'organes pour la greffe du sujet adulte dans le monde occidental. La source offrant le plus grand potentiel d'élargir le pool de greffons est celle de donneurs à critères élargis, également appelés donneurs marginaux.

Greffons marginaux

Bien qu'une définition consensuelle ne soit pas encore établie, les donneurs marginaux comprennent un large éventail de donneurs aux caractéristiques défavorables, historiquement associés à un moindre taux de survie du patient et du greffon, comparées à des greffons « optimaux ». Il s'agit notamment de donneurs âgés, de foies stéatosiques, donneurs avec hypernatrémie, donneurs en état de mort circulatoire, et autres[2].

L'utilisation de greffons issus de donneurs plus âgés est associée à un risque accru de mortalité et de perte du greffon, en particulier chez les patients atteints d'hépatopatie virale C[2,139]. Cependant, chez certains patients d'excellents résultats peuvent être obtenus. Des greffons atteints de stéatose micro- ou macrovacuolaire <30% sont considérés adaptés pour la transplantation, avec des résultats superposables aux greffons non stéatosiques[2,139]. Des greffons avec une stéatose macrovacuolaire modérée (30%-40%) peuvent entraîner des résultats acceptables chez certaines associations donateurs-receveurs[2,139]. Des greffes avec macrostéatose

sévère ne devraient pas être utilisés car ils sont associés à risques accrus de perte de greffon et de mortalité[2,139].

Les greffons éligibles à une transplantation dans les pays occidentaux sont essentiellement issus de donneurs décédés en état de mort encéphalique (DDME ou DBD), avec un intérêt croissant pour les donneurs en état d'arrêt circulatoire (DDAC ou DCD) comme source supplémentaire d'organes pour la transplantation. Cette dernière catégorie représente un sous-groupe des greffons à critères élargis. Selon le cadre dans lequel la mort circulatoire se produit, le DDAC peut être classé en utilisant les critères de Maastricht[140,141]. Le donneur DDAC de type II a été développé notamment en Espagne et en France[142], mais après des résultats décevants en termes de complications graves entrainant la perte de greffon, le programme de DDAC Maastricht II a été abandonné sur l'ensemble du territoire français[93]. Des meilleurs résultats sont reportés par des DDAC de type Maastricht III, avec des survies des greffons à 1 et 5 ans de 75% et 54% respectivement[143], même si gravés d'un taux de dysfonction précoce du greffon significativement plus élevé (71% vs 41%) que les TH à partir d'un greffon cadavérique[144]. Les résultats des greffes à partir d'un greffon DDAC ne sont pas encore optimales, et l'utilisation combinée de la machine à perfusion pour minimiser l'impact de l'ischémie chaude prolongée semble ouvrir des perspectives intéressantes[145].

2.4.4 TRANSPLANTATION HEPATIQUE (ACTE CHIRURGICAL)

Depuis son introduction dans la pratique clinique en 1963, la technique de transplantation hépatique (orthotopique) s'est progressivement affinée. La technique originale comprenait la résection de la veine cave inférieure (VCI) du receveur avec un by-pass extracorporel veino-veineux. Au fil du temps, des variantes techniques et de l'optimisation anesthésique, la transplantation hépatique a été progressivement réalisée avec des techniques d'hépatectomie préservant la VCI du receveur, sans recours à un pontage veino-veineux et avec ou sans l'utilisation d'un shunt porto-cave temporaire. Quelle que soit la technique exacte et le type de greffon utilisé, la TH se caractérise par trois étapes : la phase d'hépatectomie totale, la phase anhépatique et la phase d'implantation.

Hépatectomie totale

La gamme et la forme des incisions abdominales en transplantation hépatique sont similaires à celles de la chirurgie hépatique[7]. Une enquête récente[128] a indiqué comment les deux incisions les plus populaires soient en T inversé (incision

transversale bilatérale avec refend verticale) et en « Mercedes » dans 70 % des programmes de greffe. D'autres alternatives sont l'incision transversale droite avec extension verticale jusqu'à la xiphoïde (en forme de J ou de L, connue sous le nom de Makuuchi modifié) et l'incision médiane[146]: la présence d'une telle gamme de choix suggère que toutes sont pratiques, y compris la voie mini-invasive[147](quoique cette dernière relève que d'un *case-report*).

Après l'incision, les éléments du pédicule hépatique sont progressivement disséqués (voie biliaire, artère hépatique).

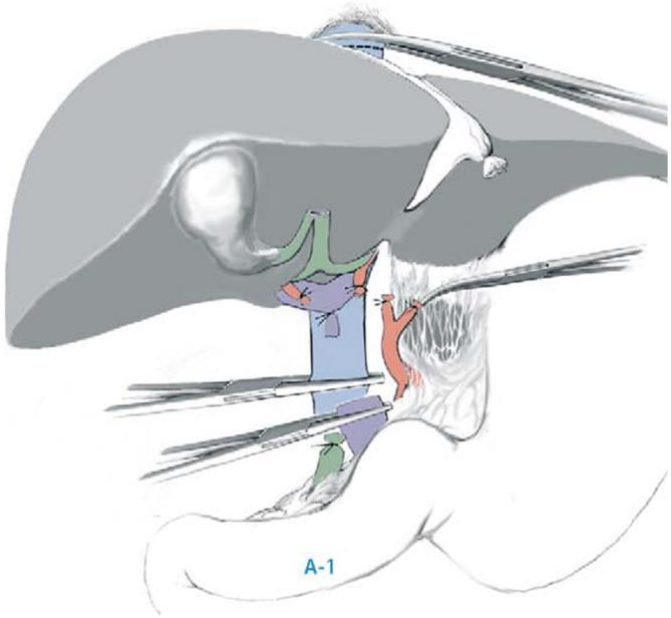


Figure 7 *Représentation schématique de la dissection des éléments pédiculaires, pendant la phase d'hépatectomie totale. D'après Sarr et al.*[148]

Plus en détail, la dissection de l'artère hépatique commune et propre est suivie de la ligature et section des branches gauche et droite. Le canal cholédoque est disséqué le plus haut possible, en préservant une quantité adéquate de tissu l'entourant pour éviter la dévascularisation et l'ischémie de la voie biliaire. La veine porte est complètement libérée de son environnement cellulovasculaire, du bord supérieur du pancréas jusqu'au hile. Toutes ces étapes doivent être effectuées avec une attention particulière, car l'hypertension portale et la dilatation consécutive du lit vasculaire comportent des vaisseaux plus fragiles et sujets aux saignements[148].

A ce propos, et pour réduire la pression portale pendant la phase d'hépatectomie, la réalisation d'un shunt porto-cavo temporaire (anastomose porto cave ou APC) peut faciliter la dissection de la VCI retro hépatique[149,150].

A ce stade de l'intervention, les plans de dissection sont différents pour la greffe « classique » (avec résection et remplacement de la VCI) et pour la greffe avec préservation de la VCI (technique du piggyback)[148]. Cette dernière est plus exigeante mais a l'avantage d'éviter l'interruption du retour veineux cave, et d'un temps d'ischémie chaude plus court lors de l'implantation, car avec le piggyback une seule anastomose latéro-latérale (et non deux) doit être réalisée[148].

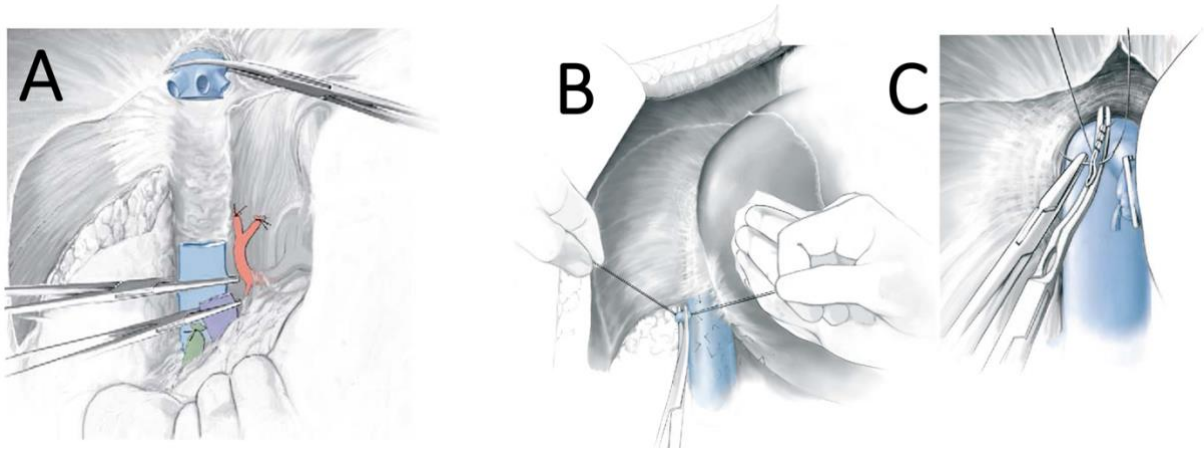


Figure 8 *Représentation schématique des plans de dissection en cas de (A) remplacement ou (B et C) préservation de la veine cave inférieure. D'après Sarr et al.*[148]

Tant pour l'approche classique que pour la technique de préservation cave, la pression veineuse centrale doit être maintenue aussi basse que possible, pour minimiser le saignement pendant la dissection de la VCI rétrohépatique et des veines Spigeliennes.

Phase anhépathique

Avant l'achèvement de l'hépatectomie totale, l'hémostase de la région rétro péritonéale est réalisée à l'aide de la bipolaire, d'un coagulateur à argon ou par des points électifs[148].

- La technique classique avec résection de la VCI prévoit une section après ligature ou clampage du tronc porte le plus haut possible dans le hile. La VCI supra et infra hépatique est enfin sectionnée sur deux clamps (*Satinsky* ou équivalents).
- La technique de préservation de la VCI (ou *piggyback*) comprend le clampage et division de la veine porte (en cas de non réalisation d'une APC), suivie de

l'hépatectomie totale de la gauche vers la droite avec la section progressive du tronc veineux commun et de la veine hépatique droite.

Le foie natif est ainsi reséqué.

Implantation

Après avoir introduit le greffon dans la cavité abdominale, l'anastomose cave est réalisée en premier. En fonction de l'étape précédente, sera réalisée un'anastomose termino-terminale supra hépatique et infra hépatique (remplacement de la VCI), soit une anastomose latéro-latérale terminalisée (*piggyback*)[148].

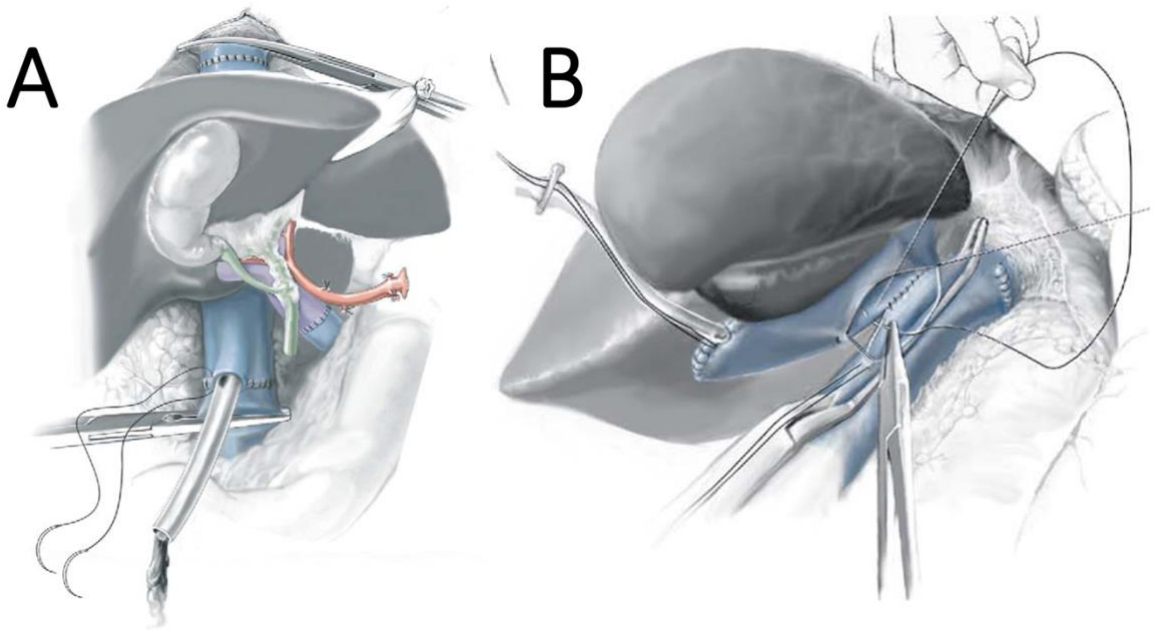


Figure 9 *Représentation schématique d'une transplantation avec remplacement de la veine cave inférieure (A) et préservation de la veine cave inférieure (B) avec anastomose en Piggyback. D'après Sarr et al.*[148]

A partir de ce stade, les étapes suivantes sont identiques pour la technique classique et pour le piggyback[148].

Après avoir coupé la veine porte du greffon à une longueur congruente, une anastomose termino-terminale est réalisée. Une purge par du sérum physiologique et « au sang » par un très court déclampage sont essentielles pour éliminer des éventuels caillots. L'anastomose est réalisée avec un facteur de croissance adéquat (*growth factor*)[148]. En fonction des habitudes locales, mais surtout du temps d'ischémie froide et chaude, ainsi que l'état du receveur et la qualité du greffon, il est possible de réaliser un déclampage pour assurer la réperfusion du greffon à ce stade, ou

poursuivre avec la réalisation de l'anastomose artérielle[148]. La phase de réperfusion du greffon commence par le déclampage de la VCI, avec une réperfusion séquentielle de la veine porte et de l'artère hépatique. Par la suite, l'anastomose biliaire sera réalisée (término-terminale ou hépaticojejunale).

Un drain abdominal prophylactique après une TH a traditionnellement été utilisé pour surveiller les saignements postopératoires, une éventuelle fistule biliaire, mais surtout le drainage de l'ascite. Leur utilisation est encore largement répandue, comme le révèlent deux enquêtes[128,151]: 86 % à 90 % des centres répondants réalisent un drainage abdominal systématique.

2.4.5 TRANSPLANTATION HEPATIQUE (CONSIDERATIONS ANESTHESIOLOGIQUES)

Un accès veineux de gros calibre (périphérique et/ou central) et fonctionnel est nécessaire pour l'administration de solutés intraveineux (IV), de produits sanguins et de vasopresseurs. Un cathéter veineux central (CVC) est habituellement mis en place dans le territoire jugulaire interne avant l'incision chirurgicale.

La surveillance cardiovasculaire comprend un cathéter intra-artériel, un CVC pour surveiller la pression veineuse centrale (PVC), et dans certains cas, un cathéter artériel pulmonaire pour surveiller le débit cardiaque en continu, la pression artérielle pulmonaire (PAP), et la saturation veineuse centrale. Un monitorage hémodynamique par échocardiographie trans-œsophagien (ETO) peut être discuté au cas par cas et en cas d'absence de contre-indications (varices œsophagiennes).

L'induction anesthésique en séquence rapide est généralement utilisée pour procéder à l'intubation endotrachéale et mettre en place la ventilation mécanique, en raison d'un temps de jeûne insuffisant (contexte de chirurgie non programmée) et/ou d'une augmentation de la pression intra-abdominale due à une ascite modérée ou sévère.

Les propriétés des agents anesthésiques à courte durée d'action à élimination rapides, ainsi que la titration de tous les agents anesthésiques dans le cadre d'une anesthésie balancée, sont les garants d'un réveil rapide avec des effets résiduels minimes.

L'intervention chirurgicale majeure et l'administration concomitante d'un traitement immunosuppresseur expliquent la nécessité d'une prophylaxie antibiotique per-opératoire; cependant, ses modalités peuvent varier considérablement d'un centre à l'autre. En effet, les bactériémies, les infections du site opératoire (ISO) et les infections de parois après une transplantation hépatique augmentent la mortalité, la morbidité ou

allongent le séjour à l'hôpital et sont susceptibles d'augmenter les coûts globaux associés à la transplantation[152–155].

L'administration de vasopresseurs pour maintenir la stabilité hémodynamique est généralement nécessaire pendant l'induction et/ou lors de la réperfusion. Des agents inhalés ou IV peuvent être utilisés pour entretenir l'anesthésie générale.

Les transfusions de globules rouges (GR) et d'autres produits sanguins, y compris le plasma frais congelé (PFC), le concentré de fibrinogène, et les concentrés plaquettaires sont généralement nécessaires (mais pas systématiques) lors d'une transplantation hépatique. Ils doivent suivre les recommandations concernant les cibles poursuivies. La récupération de sang peropératoire à l'aide d'un système de sauvegarde (*cell saver*) est généralement utilisée comme modalité d'épargne transfusionnelle.

Une cible de PVC de 7 à 10 mmHg est souvent proposée. Pour être plus précis, une méta-analyse récente[156] se concentrant sur une stratégie de perfusion libérale versus restrictive a mis en évidence une association entre la stratégie restrictive et une moindre incidence de complications pulmonaires, une réduction de la durée de ventilation mécanique et des pertes sanguines, sans pour autant impacter l'incidence d'insuffisance rénale aigue. Cependant, compte tenu des variations à la réponse au remplissage en fonction de la sévérité de la cirrhose[157], ainsi que le large éventail de variations hémodynamiques pendant les trois phases de la TH[158,159], une stratégie "figée" peut ne pas être la meilleure option.

Concernant le remplissage vasculaire, des solutions de cristalloïdes balancés (par exemple, le Ringer-Lactate®) sont à considérer, tout comme l'albumine à 5%. Les patients présentant une coagulopathie documentée, peuvent recevoir en priorité des PFC.

En vue de la réperfusion du greffon du donneur, les gaz sanguins artériels et les électrolytes doivent être contrôlés et l'hyperkaliémie doit être traitée de manière agressive avant le déclampage.

La phase néohépatique commence après que le greffon ait été réperfusé et comprend la reconstruction biliaire, l'hémostase chirurgicale, la fermeture de la paroi abdominale et la planification de l'extubation. Si la perfusion et la fonction du greffon est adéquate, les taux de lactates et les besoins en vasopresseurs diminuent au fil des heures.

Des complications peropératoires sévères nécessitant un traitement rapide peuvent survenir :

- Le syndrome post-réperfusion (diminution de la PAM de plus de 30 %, survenant dans les cinq minutes suivant la réperfusion et perdurant plus d'une minute) peut entraîner une insuffisance cardiaque droite, une hypotension sévère ou une hyperkaliémie menaçante.
- Des exacerbations de l'hyperkaliémie et de l'acidose métabolique sont possibles lors de la réperfusion et doivent être traitées de manière agressive. D'autres anomalies métaboliques comprennent l'hyponatrémie et les dysglycémies.
- Un événement thrombo-embolique pulmonaire ou intracardiaque (très rare) est rapidement confirmé ou infirmé par l'ETO.
- L'arrêt cardiaque survient le plus souvent peu de temps après la réperfusion en raison d'une hyperkaliémie ou de complications thromboemboliques.

Les complications postopératoires peuvent inclure :

- Saignements dus à une coagulopathie persistante résultant d'un dysfonctionnement précoce du greffon ou d'une hémostase chirurgicale inadéquate. Des tests viscoélastiques délocalisés peuvent être utilisés pour différencier ces causes. Dans certains cas, un packing chirurgical doit être considéré, avec une reprise dès la stabilisation de la coagulopathie.
- La cirrhose étant associée à un risque hémorragique accru (diminution du TP et de la numération plaquettaire), les patients sont supposés être «naturellement» anticoagulés. De plus, étant donné l'incidence élevée de complications hémorragiques, la thromboprophylaxie pharmacologique après TH n'est pas utilisée en routine, en dehors de la période à haut risque post-opératoire immédiat en soins critiques. Ce dogme est de plus en plus remis en cause par le nouveau paradigme fondé sur le concept de « l'hémostase rééquilibrée » : les patients atteints d'une maladie du foie peuvent avoir un équilibre hémostatique instable en raison de modifications concomitantes des voies pro- et anti-hémostatiques, comme le suggèrent la survenue à la fois de de complications hémorragiques et thrombotiques[160].
- Les patients bénéficiant d'une TH sont exposés à un risque élevé d'hypothermie per-opératoire (<36°C) en raison de l'importance de l'exposition viscérale, de la durée de la chirurgie, de la perfusion de grands volumes de liquides et de transfusions, de l'exclusion hépatique (organe à métabolisme élevé) et de son remplacement par un greffon conservé dans des solutions froides. Les principales conséquences de l'hypothermie périopératoire sont un risque accru

d'arythmies cardiaques, de décompensation de coronaropathie, de coagulopathie, d'infections du site opératoire et d'altération du métabolisme des médicaments[161,162].

- L'hyperglycémie périopératoire est une constatation fréquente au cours de la TH, conséquente d'une exacerbation de la résistance à l'insuline induite par une intervention chirurgicale lourde, et aggravé par le « diabète hépatogénique » du foie natif cirrhotique, les phases anhépatiques et de réperfusion, le type de greffon, les stéroïdes à fortes doses et les immunosuppresseurs[163–166]. Plusieurs études rétrospectives, basées sur des cohortes monocentriques[167–173] et un registre national de TH[174] incluant au total plus de 4 900 patients, a également rapporté une association entre une hyperglycémie d'apparition récente non contrôlée (150-200 mg/dL) et de mauvais résultats cliniques, y compris de mortalité, insuffisance rénale aiguë, septicémie, rejet, durée d'hospitalisation et risque de réadmission après TH.

À l'instar de la chirurgie majeure, l'extubation précoce après TH a progressivement gagné en popularité : après une courbe d'apprentissage relativement abrupte et une confiance croissante[175], certains centres[176–178] ont signalé jusqu'à 70 % de taux de patients candidats à une extubation précoce après TH. Il est intéressant de noter qu'il n'existe pas de définition claire de « extubation précoce » avec un intervalle de temps entre la fin de la greffe et l'extubation allant de quelques minutes à 3 - 8 heures. Cependant, l'extubation précoce n'est pas toujours souhaitable, comme par exemples chez les malades présentant des décompensations de comorbidités sévères, un greffon limite, ou un saignement persistant pouvant nécessiter une ré-exploration chirurgicale dans les 36 heures suivantes. Globalement, les critères habituels d'extubation s'appliquent également dans le cadre de la TH, et leur présence doit être évaluée de manière rapprochée afin de ne pas retarder l'extubation, et par la-même, réduire au maximum la durée d'exposition au risque inhérent à la ventilation mécanique.

Bien que la douleur postopératoire après transplantation hépatique soit considérée comme étant moins sévère qu'en chirurgie hépatique[179,180], une analgésie adéquate doit être fournie pour permettre une mobilisation précoce et une récupération postopératoire rapide. Cependant, étant donné le rôle du foie dans le métabolisme et l'excrétion du médicament, une mauvaise récupération du greffon peut contribuer à un métabolisme, une concentration plasmatique et une clairance imprévisible des antalgiques. Pour la gestion postopératoire de la douleur, sont généralement proposés

des opioïdes systémiques avec une technique d'analgésie contrôlée par le patient (PCA) associés à d'autres antalgiques de palier I et II de l'OMS, de manière multimodale et synergique.

2.4.6 LA GESTION POSTOPERATOIRE PRECOCE APRES TRANSPLANTATION HEPATIQUE.

Un drain abdominal prophylactique après transplantation hépatique a traditionnellement été utilisé pour surveiller les saignements postopératoires, les fuites biliaires, drainer l'ascite. Leur utilisation est encore largement répandue, comme le révèlent deux enquêtes[128,151]: 86 % à 90 % des centres répondants réalisent un drainage abdominal systématique.
Il n'y a aucune preuve directe concernant la supériorité de la nutrition orale précoce par rapport à la nutrition entérale (NE) ou la nutrition parentérale (NP) dans le cadre de la TH. Les directives de l'ESPEN recommandent de commencer une alimentation normale et/ou une NE dans les 12 à 24 h après la greffe pour minimiser le taux d'infections[121]. Après la phase postopératoire aiguë, le besoin en apport énergétique doit être de 30-35 kcal x kg^{-1} x d^{-1} (ex. pour un patient de 70 kg : 2100-2450 Kcal par jour)[121]. L'occurrence de l'iléus postopératoire après TH est sous-estimée, et peut empêcher une alimentation postopératoire précoce, aggravant ainsi la malnutrition et la fragilité des patients. Dans cette optique, sa prévention pourrait être un objectif clé des protocoles de récupération améliorée.

L'alitement prolongé est associé à l'aggravation de l'atrophie musculaire, à une perte de force musculaire[181] et un séjour prolongé en unité de soins critiques[182]. Cependant, il n'y a pas de consensus concernant la nécessité et surtout les modalités optimales de la mobilisation précoce des malades.

Comme abordé dans le chapitre du bilan pré-greffe, une connaissance insuffisante de la maladie et la complexité des prescriptions médicales sont corrélées à une moindre adhésion thérapeutique[99,183], cette dernière étant associée à un risque accru de rejet de greffe et de complications post-greffe[222]. Pour cette raison, des programmes d'éducation après la transplantation hépatique sont nécessaires. Il a été suggéré que les programmes d'éducation des patients devaient inclure trois types d'intervention : l'éducation personnalisée, l'intervention comportementale et le soutien psychologique[96]. Les objectifs sont de fournir des informations assurant la sécurité du patient, des connaissances adaptées pour aider les patients à choisir des méthodes

de gestion du stress et à accepter leur nouvelle maladie chronique. L'implication d'un pharmacien clinicien et des séances collectives avec des patients experts peuvent être envisagées.

2.4.7 LA TRANSPLANTATION HEPATIQUE COMME PARCOURS DE SOINS COMPLEXE

Comme il a été détaillé tout le long des paragraphes précédents, plusieurs éléments contribuent à la complexité de la prise en charge d'un malade bénéficiant d'une TH: les patients receveurs sont le plus souvent poly-pathologiques, sarcopéniques, et souffrent des complications de l'insuffisance hépatique terminale[120,133,184,185] ; la procédure chirurgicale nécessite d'une expertise technique hépatobiliaire et vasculaire[2,133,185], comporte un risque de complications post-opératoires immédiates significatif (non fonction primaire 3%[186], vasculaires 3-13%[185,187,188] biliaires 37.5%[187,189]), et l'introduction précoce d'une immunosuppression per- et post-opératoire peut exposer les patients à des complications spécifiques infectieuses (50%)[190,191], hématologiques, neurologiques (10-60%)[192,193] ou rénales (63%)[194,195]. Enfin, l'immunosuppression impose une éducation thérapeutique. Ces différentes prises en charge nécessitent l'intervention pré-, per- et post-opératoire de plusieurs spécialistes issus de différents domaines : chirurgie, anesthésie-réanimation, hépatologie[2,196]. Cette collaboration pluridisciplinaire rend le parcours de soin de la TH particulièrement exigeant, conditionne les résultats à court terme de la TH[194], et repose sur un suivi rapproché et coordonné[197], pour rapidement détecter et éviter tout événement indésirable grave.

Pour toutes ces raisons, la TH ne peut pas être simplement réduite à une intervention chirurgicale majeure, mais est plutôt à considérer dans son ensemble comme un projet thérapeutique dont le parcours de soins complexe nécessite une mobilisation importante de ressources humaines et financières[1].

L'articulation du parcours peut en partie expliquer que la durée moyenne de séjour (DMS) de ces malades soit très hétérogène (de 8 à 31 jours) dans la littérature, étant également dépendante des conditions socio-économiques et des pratiques médicales variables dans différents centres et pays[1,195,198,199]. Ainsi, la DMS « classique » n'apparait pas pertinente comme indicateur standardisé de récupération post-opératoire.

2.4.8 PRISE EN CHARGE HABITUELLE DE LA PERIODE PERI-OPERATOIRE D'UNE TRANSPLANTATION HEPATIQUE.

La prise en charge standard de la periode péri-opératoire d'une TH « hors approche RAC » repose sur des protocoles hétérogènes, et s'appuie souvent sur des habitudes de centre ou de service, basées sur des approches empiriques et/ou des données très éparses de la littérature. Si les modalités techniques chirurgicales per-opératoires optimales ont été mieux décrites et adoptées par la plupart des centres[2], les modalités de prise en charge chirurgicale, anesthésique, réanimatoire et médicale péri-opératoires restent très hétérogènes. Plusieurs revues de la littérature[200,201] attestent de cette hétérogénéité et restent elles-mêmes très imprécises quant à la gestion de nombreux aspects péri-opératoires de la TH, tels que la gestion des dispositifs de drainages abdominaux, de l'analgésie péri-opératoire, du délai d'extubation, du délai de reprise de la mobilisation active du patient, du retrait des cathéters (artériels, veineux centraux et périphériques) et des sondes (vésicale, gastrique), de la reprise de l'alimentation.

Actuellement, la prise en charge standard péri-opératoire d'une TH n'est pas entièrement systématisée. Cependant, elle repose globalement sur les éléments suivants :

- Consultations et bilan pré-TH suivis de mise sur liste d'attente de TH
- Le jour de la TH : admission, bilan sanguin, jeûne pré-opératoire et prémédication
- Au bloc opératoire: induction et entretien anesthésique reposant sur une anesthésie balancée (hypnotiques intraveineux et/ou halogénés inhalés, analgésique morphinique et curares).
- Transplantation hépatique orthotopique : hépatectomie totale, anhépathie et implantation du greffon (entier ou partagé).
- Transfert en réanimation systématique, pour suite de la prise en charge
- Arrêt des sédations et extubation après vérification de l'absence d'hémorragie (premier bilan biologique, hémostase, débits des drainages), obtention d'une normothermie, d'un relai par une analgésie multimodale et l'obtention des critères habituels d'extubation (critères hémodynamiques, respiratoires et neurologiques).
- Le délai d'extubation est laissé au choix des réanimateurs sans consensus. Même si des études ont démontré un bénéfice de l'extubation précoce (sur table ou dans les 3 heures suivant la chirurgie) sur la réduction de la morbidité

respiratoire post TH (réduction de l'incidence des pneumonies post-opératoires notamment), le caractère monocentrique et/ou uniquement rétrospectif de ces études ne permet pas la généralisation de cette pratique de façon systématique[201].

- Analgésie multimodale par voie systémique jusqu'à reprise du transit permettant le relai *per os*.
- Ablation de la sonde naso-gastrique dès reprise de transit (apparition des bruits hydro-aériques à l'auscultation, et constatation des premiers gaz) ou débit < 500ml/24h.
- Reprise de l'alimentation per os progressive (eau, yaourt/compote, repas léger) dès la reprise du transit et en fonction de la tolérance du patient.
- Ablation des dispositifs de drainages abdominaux quand le débit reste inférieur à 100ml/24h, ou à discrétion du chirurgien.
- Mobilisation active dès que possible. Elle est basée sur le contrôle de l'analgésie du patient et sur les possibilités logistiques de mise en place, souvent limitées, et variables dans les centres, et selon la disponibilité du personnel paramédical incluant IDE et kinésithérapeutes.
- Mise au fauteuil dès que possible.
- Ablation du cathéter artériel dès que possible (stabilité hémodynamique et espacement des bilans biologiques sanguins).
- Ablation du ou des cathéters veineux centraux dès que possibles (stabilité hémodynamique, voie veineuse périphérique disponible et fonctionnelle).
- Ablation des cathéters veineux périphériques dès que possible (absence d'indication d'administration d'un médicament par voie intraveineuse).
- Ablation de la sonde vésicale dès que possible (stabilité hémodynamique, absence de défaillance rénale, patient pouvant gérer ses besoins mictionnels).
- Transfert en unité de soins continus (USC) dès que possible en fonction de la disponibilité des places.
- Transfert en salle d'hospitalisation d'hépatologie ou de chirurgie hépatobiliaire en fonction des places disponibles.
- Sortie du patient à domicile dès que possible, se basant sur des critères de sortie hétérogènes, et variant en fonction du centre de prise en charge (autonomie du patient, dispositif relais à domicile, entourage familial, observance et éducation thérapeutique sur la prise des immunosuppresseurs, bilan biologique, absence de sepsis).

3 PROJET DE RECHERCHE : LA RAC EN TRANSPLANTATION HEPATIQUE

3.1 HYPOTHESES DE LA RECHERCHE

L'ensemble de ce travail de recherche repose sur l'hypothèse qu'un protocole de RAC appliqué à la TH pourrait améliorer la prise en charge des malades notamment en termes de suites post-opératoires et de durée de séjour/récupération fonctionnelle.

A partir de ces points, et basés sur les données disponibles en littérature, nous avons établi un plan de recherche en partie s'inspirant les étapes proposées par les recommandations IDEAL[202], portant sur l'évaluation de la recherche en chirurgie. Trois freins à notre recherche ont rapidement été identifiés : la faisabilité de transposer un protocole existant dans un domaine de la chirurgie (hépatique) à un autre (transplantation), l'absence de définition claire de marqueurs post-opératoires dits « *outcomes* » et l'absence de définition d'une récupération fonctionnelle du malade mais surtout du greffon. En effet, l'une des originalités de la transplantation, c'est qu'il faut à la fois évaluer un malade et un greffon, et que des critères spécifiques doivent être définis pour chacun.

3.2 EVALUATION DE L'INNOVATION EN CHIRURGIE

Lorsqu'une innovation thérapeutique est développée, son évaluation est indispensable. Quand il s'agit d'un médicament, quatre phases d'évaluation distinctes et successives sont bien définies[203].

- Phase I : étude pharmacocinétique de la molécule à l'étude et analyse de la toxicité sur l'être humain. Cette phase est menée sur volontaires sains.

- Phase II : recherche de la plus petite dose efficace, effets secondaires, toxicité, par un essai prospectif de petite taille sur une population cible sélectionnée (preuve du concept chez des patients atteints de la pathologie cible du médicament).

- Phase III : comparaison de l'efficacité du nouveau médicament par rapport au traitement de référence et/ou à un placebo, par un essai randomisé de grande taille.

- Phase IV : études de pharmacovigilance/pharmacoépidémiologie, à grande échelle et sur le long terme.

Ce processus est optimal pour un médicament : par définition sa dose, mode d'administration et conditionnement (gélules, sirop, gouttes, comprimés...) sont bien définies, constantes, mesurables et reproductibles. A partir de la phase II et systématiquement pendant la phase III, les études planifiées sont des essais randomisés et contrôlés (ERC)[204], pouvant offrir le plus haut niveau de preuve.

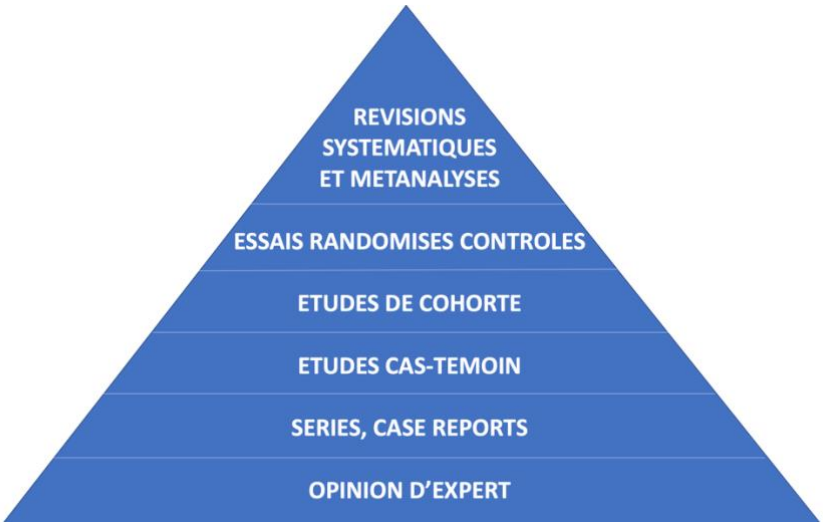


Figure 10 *Exemple de hiérarchie du niveau de preuve*[204]*.*

Cependant, lorsque la structure d'un traitement est plus compliquée et articulée qu'un médicament, on parle d'*intervention complexe*[202]. Les innovations du domaine chirurgical, par exemple, en font partie : une intervention chirurgicale, pour bien qu'elle soit standardisée même après la courbe d'apprentissage, ne sera pas réalisée exactement de la même manière par deux chirurgiens, ni par le même chirurgien sur deux malades différents. Les variations au cours d'une opération sont en effet courantes et peuvent influencer les taux de réussite. Lors de la comparaison des opérations, il est donc nécessaire de définir clairement les limites de la variation technique acceptable[205]. Une description standard peut être nécessaire, proscrivant toute modification. Si les définitions ne sont pas précises, les traitements/interventions délivré(e)s peuvent se chevaucher, alors que dans les essais de médicaments, les traitements sont généralement simples à définir exactement. Tous ces limites ralentissent la diffusion des ERC en chirurgie, et ont peu de parallèles dans les essais de médicaments, dont le modèle (du développement clinique du médicament) n'est pas approprié pour la chirurgie[202].

Pour toutes ces raisons un groupe de méthodologistes et chirurgiens ont proposé en 2009 des recommandations adaptées au cadre chirurgical par le développement des cinq phases du processus d'innovation en chirurgie, résumées par l'acronyme IDEAL (*Innovation*, *Development, Exploration, Assessment, Long-term study*)[202]. A chaque phase correspondent des *designs* d'étude différents : l'ERC est l'une des alternatives, mais pas la seule.

	1 Idée	2a Développement	2b Exploration	3 Évaluation	4 Études à long terme
But	Preuve de concept	Développement	Découverte	Evaluation	Surveillance
Nombre et types de patients	Hautement sélectionnés	Peu, sélectionnés	Plusieurs, élargissement des indications	Plusieurs, élargissement des indications (bien définies)	Tous éligibles
Nombre et types de chirurgiens	Très peu; innovateurs	Peu; innovateurs, convaincus de la première heure	Plusieurs, innovateurs, majorité précoce	Nombreux, large majorité	Tous éligibles
Type de Production	Description	Description	Mesure; comparaison	Mesure; informations complètes pour les non-participants aux ERC	Description; audit; assurance de qualité; ajustement du risque
Intervention/Procédure	Procédure en évolution, lancement de la procédure	Procédure en évolution, développement de la procédure	Procédure en évolution, perfectionnement de la procédure; apprentissage communautaire.	Stable	Stable, standardisées
Méthode	Case reports structurés	Etudes prospectifs de développent	Base de données de recherche, ERC de faisabilité	ERC avec ou sans modifications, design alternatifs	Registre; base de données; rapports de cas rares
Résultats	Preuve de concept	Essentiellement sécurité, réalisation technique et procédurale	Sécurité; résultats cliniques (spécifiques et gradués); résultats à court terme; résultats sur des *outcomes* centrés sur le patient ; résultats de faisabilité	Sécurité; résultats cliniques (spécifiques et gradués); résultats à moyen et long terme; résultats sur des *outcomes* centrés sur le patient ; rapport côut-efficacité	Evénements rares; résultats à long terme.

Figure 11 *Étapes de l'innovation chirurgicale.*

- L'étape 1 de *l'Innovation* se produit lorsqu'un chirurgien ou un petit groupe de chirurgiens tentent une procédure pour la première fois.
- Si les premiers résultats suggèrent des avantages, certains d'entre eux, « convaincus » de la première heure (*early adopters*), peuvent poursuivre l'innovation (Étape 2a) : pendant cette phase (stade de *Développement - Development*), l'accent est mis sur le développement technique de la procédure. Par la suite, l'attention est portée sur la sélection des indications à la procédure, sur ses avantages et inconvénients potentiels, pour monter son efficacité à un niveau optimal (Étape 2b, phase d'*Exploration*). Les premiers utilisateurs affinent leur compétence, le long de leur courbe d'apprentissage.
- Au cours de l'étape 3, la question clé est posée : cette technique est-elle meilleure que celles déjà existantes, en termes d'efficacité clinique et rentabilité? (Étape 3, phase d'*Évaluation - Assessment*). Des études définitives

sont nécessaires, mais le point de bascule peut se produire lorsqu'une procédure est suffisamment optimisée, avec un groupe de chirurgiens expérimentés dans son utilisation. Cependant, si l'opportunité d'une évaluation robuste n'est pas saisie, le risque est d'assister à une large diffusion de la procédure sans preuves suffisantes.

- Enfin (Étape 4), lorsque la procédure s'est généralisée et son utilisation est routinière, son efficacité au quotidien doit faire l'objet d'un examen rigoureux (phase d'*études à Long Terme*, correspondant aux essais de phase 4 ou pharmacovigilance). A ce stade il est possible d'affiner les connaissances sur la procédure, telles que des observations rares et des effets à long terme ; la variabilité des résultats pourrait conduire à ajuster les indications ou certains détails techniques. Seulement à ce point les résultats peuvent être généralisés à la pratique courante, et les indications peuvent être élargies[202].

Dans le cadre de la recherche faisant l'objet de cette thèse, si les quatre phases du développement du médicament n'étaient pas adaptées, les cinq étapes IDEAL ne l'étaient pas non plus : l'intérêt de la RAC avait déjà été largement montré en chirurgie digestive et hépatobiliaire, et aucun critère de jugement pour mesurer l'impact de la RAC en TH était disponible.

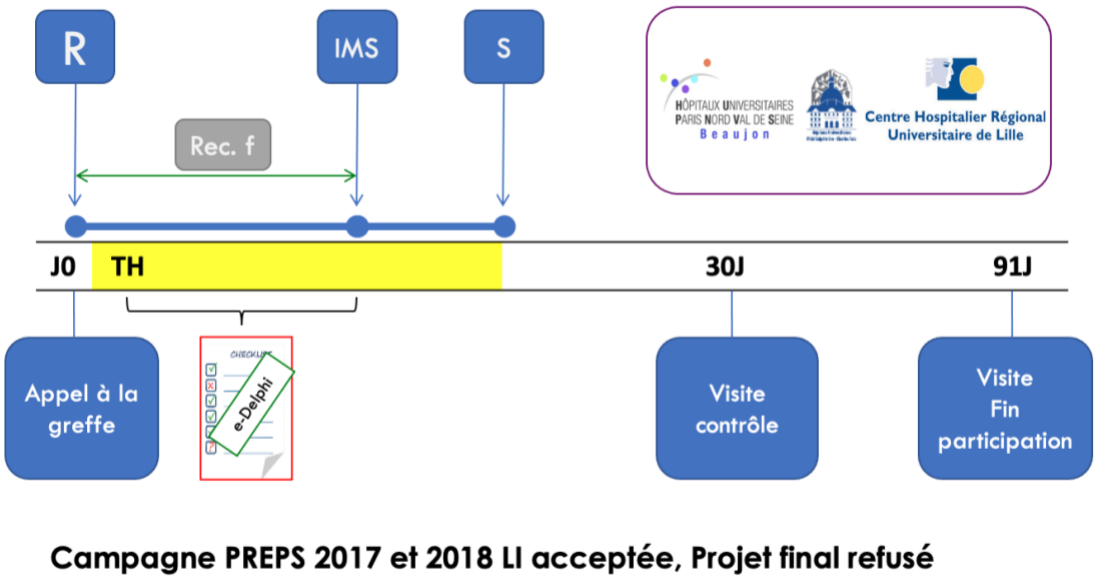
Nous nous sommes cependant calés sur les phases d'IDEAL pour construire les étapes de recherche sur la RAC en TH.

3.3 ETAPES DE LA RECHERCHE SUR LA RAC EN TRANSPLANTATION HEPATIQUE

Dans le cas de figure de la recherche en cours, une première **preuve de concept (étape 1)** a été réalisée (applicabilité de la RAC en TH sur un échantillon limité de malades), se positionnant entre la phase d'Idée (1 = *Innovation*), et Développement (2a = *Development*).

Par la suite, nous avions projeté de préparer la phase d'exploration (2b = Exploration) par une étude randomisée contrôlée de faisabilité, comparant la RAC en TH à un protocole de prise en charge habituelle, sur le taux d'adhésion au protocole (comme reflet de la faisabilité d'un tel protocole). Le protocole, ayant fait l'objet de mon mémoire de Master 2 (Recherche Clinique et Pharmacovigilance, Sorbonne Université, 2017-2018), dirigée par le Pr Scatton a été proposé pour deux années consécutives aux

campagnes de financement pour les Programmes De Recherche Sur La Performance Du Système De Soins (PREPS).



Campagne PREPS 2017 et 2018 LI acceptée, Projet final refusé

Figure 12 *résumant le projet d'étude randomisée contrôlée sur 3 centres comparant la RAC à une prise en charge standard en TH. R : randomisation, Rec. F : récupération fonctionnelle, IMS : indication médicale de sortie, S : sortie*

La lettre d'intention a été acceptée à chaque fois, mais pas le projet final. Les arguments des reviewers concernaient essentiellement le choix du critère de jugement (proposant d'évaluer la sécurité plutôt que le taux d'adhésion au protocole), et la faisabilité d'une randomisation à l'échelle du patient (proposant plutôt une randomisation à l'échelle de l'établissement/randomisation en grappe).

Les critiques des reviewers ont permis de faire évoluer la réflexion sur le projet. Concernant la question de la randomisation, déjà lors de la planification du protocole pour le PREPS des doutes raisonnables avaient émergé concernant la faisabilité, essentiellement basés sur le faible taux d'ERC publiés sur la RAC en chirurgie hépatique : la nécessité d'appliquer d'une manière homogène un protocole de soins complexe multidisciplinaire à plusieurs centres est en soi une limite majeure. Ce point, sur les difficultés logistiques et organisationnelles des ERC portant sur la RAC, nous a été confirmées ultérieurement par deux experts de la société ERAS (Pr Ljungqvist O, *Faculty Of Medicine And Health, School Of Health And Medical Sciences, Department Of Surgery, Örebro University, Örebro, Sweden* et le Pr Demartines N, *Department Of Visceral Surgery, University Hospital Chuv And University Of Lausanne, Lausanne, Switzerland*). De plus, si le design d'une étude en grappe était en effet séduisant pour minimiser l'effet de contamination entre patients, le nombre minimales de 20 centres nécessaire pour démarrer un tel essai représentait une limite (majeure) supplémentaire : seulement 16 centres de transplantation hépatique en France étaient actifs à l'époque de la soumission.

Nous avons pris du recul sur le projet, et constaté que pour la planification d'une étude d'une telle ampleur, il fallait revenir à la case de départ : les définitions.

En détail, nous avons décidé de réaliser :

- La définition d'un **critère de jugement** pertinent pour mesurer l'impact de la RAC en TH de la manière la plus appropriée **(étape 2)**.
  Trois études differentes ont permis de parvenire à la definition de la « récuperation fonctionnelle » comme critère de jugement mesurable, standardisé et consensuel traduisant la récuperation après transplantation.
- Les **recommandations officielles de la RAC en TH** pour une définition consensuelle et détaillée **(étape 3)**. Cette étape, proposée directement par la

Société ERAS, a permis de standardiser le protocole de RAC en TH, pour permettre une homogénéisation des pratiques et incrémenter sa reproductibilité. Cette étape pourrait être fondamentale en prévision d'une (large) étude de cohorte ou pour la planification d'un ERC.

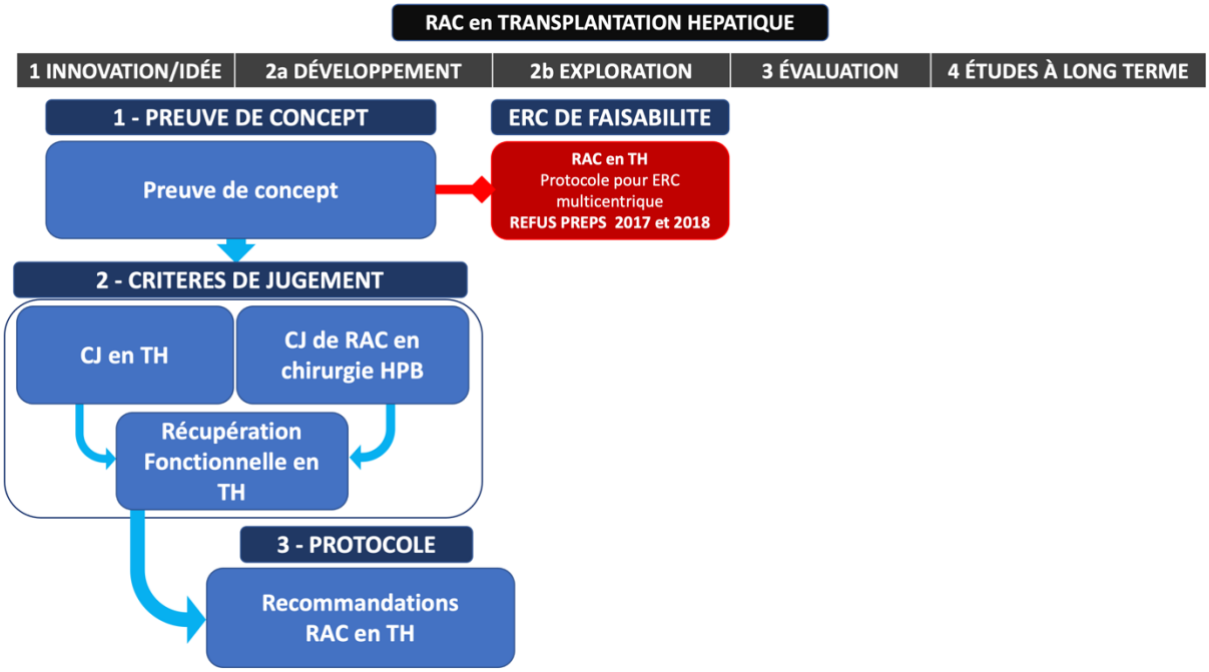


Figure 13 *résumant les principales étapes de la recherche, en rapport avec les 4 étapes du processus d'évaluation de l'innovation en chirurgie. RAC : récupération améliorée en chirurgie, TH : transplantation hépatique, CJ : critères de jugement, HPB : hépato-bilio-pancréatique, PREPS : programmes de recherche sur la performance du système de soins*.

4 TRAVAUX DE RECHERCHE

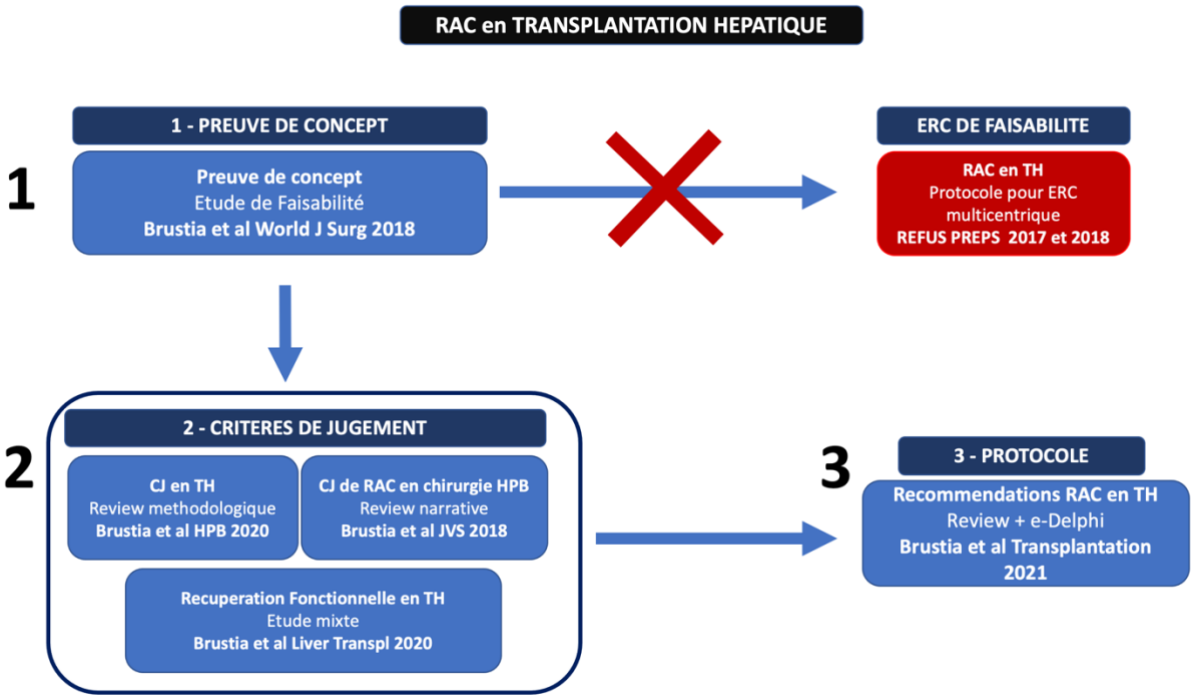


Figure 14 *résumant les trois principales étapes de la recherche (preuve de concept, critères de jugement, recommandations), avec les publications correspondantes. RAC : récupération améliorée en chirurgie, TH : transplantation hépatique, CJ : critères de jugement, HPB : hépato-bilio-pancréatique, PREPS : programmes de recherche sur la performance du système de soins*.

4.1.1 PREMIERE PHASE : LA PREUVE DE CONCEPT

Figure 14. *Preuve de concept*

La première étape a été la « *proof of concept* » par la réalisation d'une étude prospective sur un échantillon restreint de malades transplantés hépatiques et bénéficiant d'une prise en charge RAC par un protocole dérivé des recommandations en chirurgie hépatique[7] mais aussi adapté à la présence d'un greffon. Les résultats sur 30 malades (n=10 RAC vs n=20 contrôles) ont montré la sécurité et la faisabilité d'un tel programme avec un taux d'adhésion de 72.9% au protocole. Pour la première fois, des critères spécifiques de sortie inspirés des protocoles RAC en chirurgie hépatobiliaire ont été utilisés et adaptés au patient transplanté et au greffon. Même si l'objectif principal de cette étude n'était pas d'évaluer son efficacité, une réduction significative de 47% de la durée totale d'hospitalisation (9.5 vs 18 jours, p<0.0001), ainsi qu'en réanimation (3 vs 4.5 jours, p=0.005) et en chirurgie (1.5 vs 6 jours, p=0.01) a été observée par rapport à un groupe témoin appariés 1:2 sur le score de gravité préopératoire.

Les résultats de cette étude ont fait l'objet d'une publication[206]. (ANNEXE 1)

Brustia R, Monsel A, Conti F, Savier E, Rousseau G, Perdigao F, Bernard D,Eyraud D, Loncar Y, Langeron O, Scatton O. Enhanced Recovery in Liver Transplantation: A Feasibility Study. World J Surg. 2018. doi:10.1007/s00268-018-4747-y.

4.1.2 DEUXIEME PHASE : LES CRITERES DE JUGEMENT

Pour la génération d'un critère de jugement le plus approprié pour mesurer l'impact de la RAC en TH, nous avons procédé en trois étapes :

- En premier lieu ont été définis les **critères de jugement** les plus communément utilisés lors des **ERC en TH**.
- En deuxième lieu, les **critères de jugement** les plus communément utilisés pour mesurer **l'impact de la RAC en chirurgie hépatique** (le domaine le plus proche de la TH).
- La troisème étape a consisté à trouver le **commun dénominateur** entre les deux precedentes étapes, de l'adapter à la presence d'un malade et d'un greffon, et de la valider de manière consensuelle par une étude de type e-Delphi.

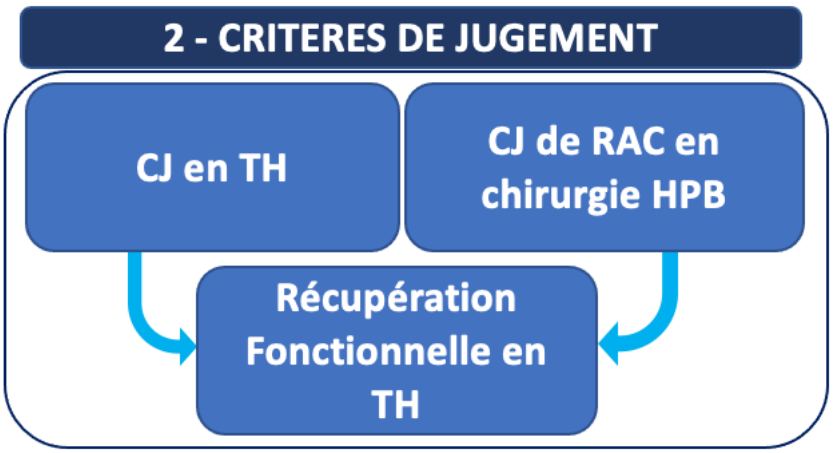


Figure 16 résumant les trois étapes pour la définition d'un critère de jugement de la RAC en TH. TH : transplantation hépatique, CJ : critères de jugement, HPB : hépato-bilio-pancréatique.

4.1.2.1 Indicateurs (critères de jugement) communément utilisés lors des essais en TH.

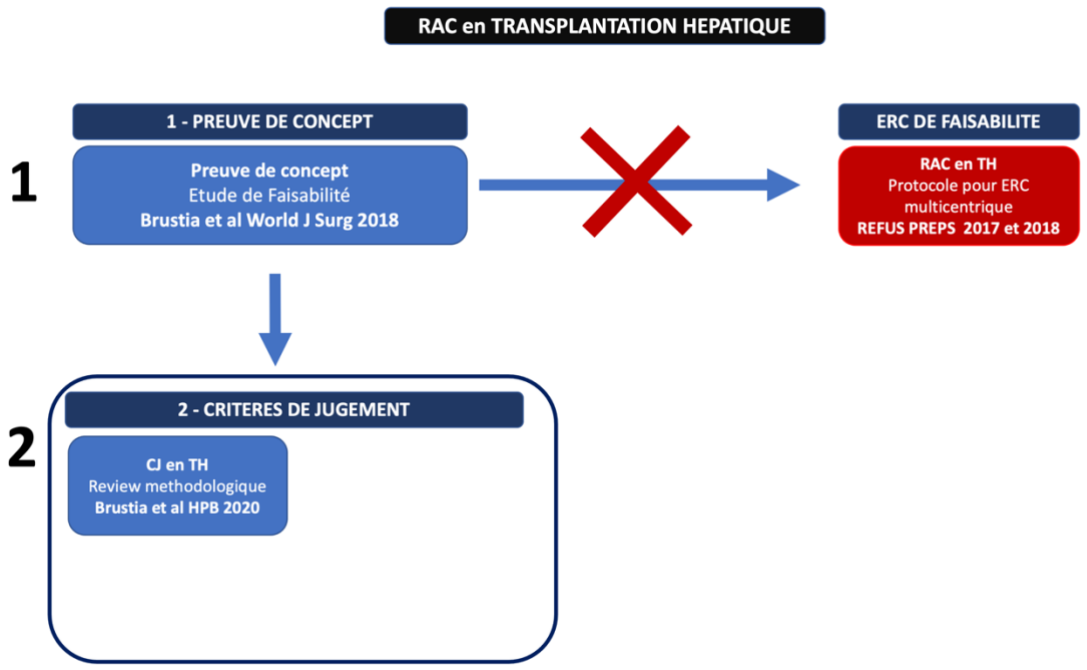


***Figure 17**. Première étape de l'analyse des critères de jugement : la greffe*

Une révision méthodologique portant sur tous les essais réalisés en TH pendant les 5 dernières années a été réalisée. Sur les 55 références incluses, la morbidité était le critère le plus fréquemment utilisé comme critère de jugement principal, suivi de mortalité, dysfonction du greffon, récupération (y compris la durée de séjour) et *patient reported outcomes* (résultats rapportés par les patients). Les critères de jugement rapportés dans les essais TH sont très hétérogènes. Une approche consensuelle pour développer un ensemble de résultats de base (COS) devrait être envisagée pour permettre des comparaisons des résultats entre les essais. Ce travail a fait l'objet d'une publication[207] (ANNEXE 2) : *Brustia R, Dechartres A, Scatton O. A methodological review of clinical outcomes reported in liver transplantation trials. HPB (Oxford). 2020Jun;22(6):833-844. doi: 10.1016/j.hpb.2019.12.010. Epub 2020 Jan 24. PMID: 31987738.*

4.1.2.2 Indicateurs (critères de jugement) pour mesurer la récupération en chirurgie hépatobiliaire.

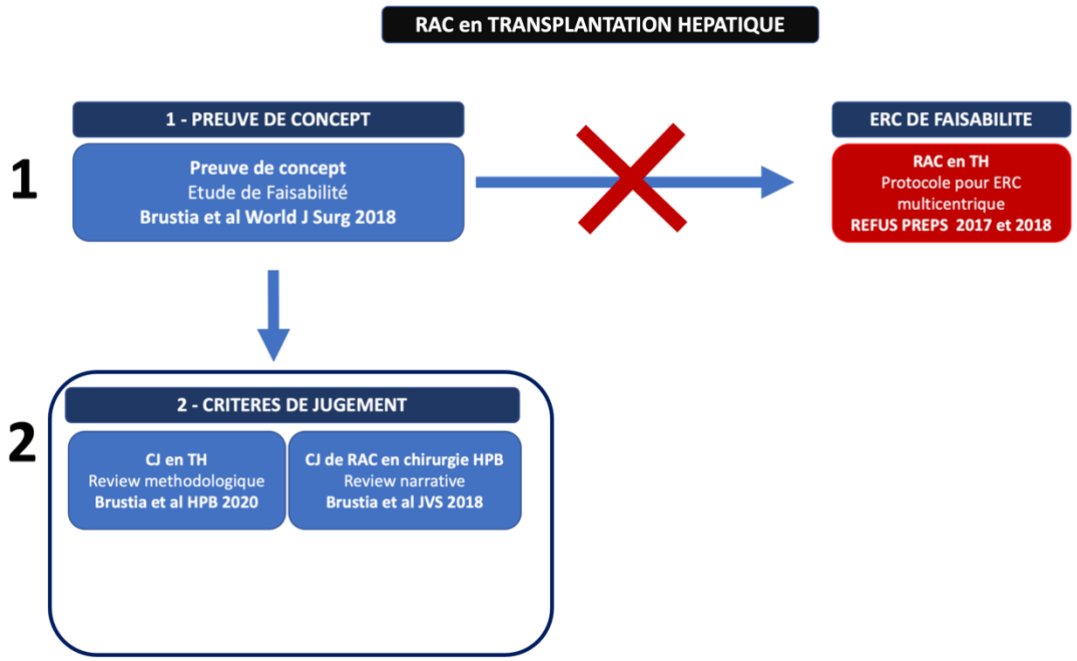


Figure 18. *Deuxième étape de l'analyse des critères de jugement : la RAC en chirurgie hépatique*

Quels indicateurs (critères de jugement) étaient les plus adaptés pour mesurer la récupération le plus objectivement possible, focalisée sur **RAC en chirurgie hépatobiliaire** ? Pour répondre à la question, une révision systématique de la littérature a été réalisée, et dont les résultats indiquent que, parmi les 18 études inclues, le critère de jugement principal majoritairement choisi a été la durée d'hospitalisation (n=13, 72%) suivi du taux de complications (n=5, 22%) et de l'impact économique (n=1, 5%). Compte tenu du fait que l'application d'un programme RAC en chirurgie hépatique semble avoir un impact sur les complications non graves (Clavien I), et que des facteurs non-médicaux peuvent augmenter de 20-40% la durée d'hospitalisation, le critère de jugement le plus pertinent semble la **durée de récupération fonctionnelle**.

Ce travail a fait l'objet d'une publication[208] (ANNEXE 3)

Brustia R, Slim K, Scatton O. Enhanced recovery after liver surgery. J Visc Surg. 2019 Apr;156(2):127-137. doi: 10.1016/j.jviscsurg.2018.10.007. Epub 2018 Nov 14. PMID: 30447936.

4.1.2.3 Définition et validation de critères de sortie après TH comme critères de jugement.

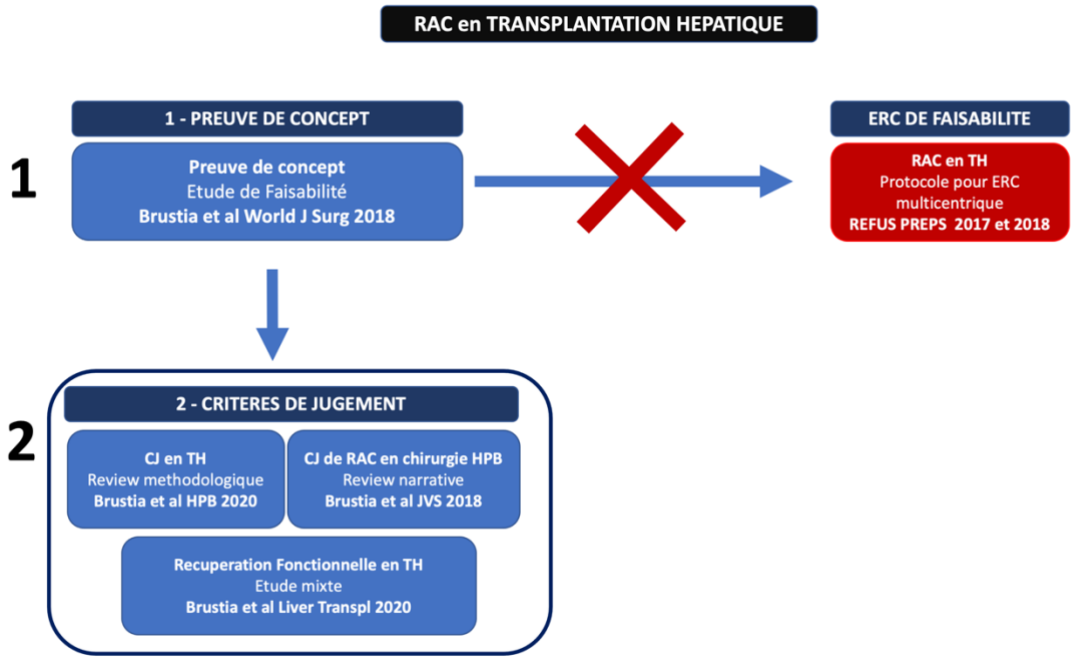


Figure 19. *Troisième étape de l'analyse des critères de jugement : définition de la récupération fonctionnelle en TH.*

Finalement, la récupération (incluant la DMS) fait partie des critères de jugement utilisés lors des ERC en TH. En même temps, la récupération fonctionnelle est considérée comme un indicateur de récupération plus pertinent que la DMS en chirurgie hépatique. En effet, la durée de séjour après TH est très variable (de 8 à 31 jours) dans la littérature, étant également dépendante des conditions socio-économiques et des pratiques médicales hétérogènes dans différents centres et pays[1,195,198,199]. Pour toutes ces raisons une étude de type mixte (combinant révision de la littérature, recherche du consensus par e-Delphi à panel restreint et élargi, ainsi qu'une étude pilote prospective) a été réalisée, permettant de **définir une liste consensuelle de critères de sortie (traduisant la récupération fonctionnelle) après transplantation hépatique**. Ce travail a été publié[209] (ANNEXE 4)

Brustia R, Boleslawski E, Monsel A, Barbier L, Dharancy S, Adam R, Dumortier J, Lesurtel M, Conti F, Scatton O; Groupe de Recherche Français en Greffe de Foie (GReF²) and the Association de Chirurgie Hépato-Pancréato-Biliaire et Transplantation (ACHBT) Collaborative Group. Definition and Prospective Assessment of Functional Recovery After Liver Transplantation: A New Objective

Consensus-Based Metric for Safe Discharge. Liver Transpl. 2020 Oct;26(10):1241-1253. doi: 10.1002/lt.25841. Epub 2020 Aug 25. PMID: 32621369.

4.1.3 TROISIEME PHASE: RECOMMENDATIONS SUR LA RAC en TRANSPLANTATION HEPATIQUE

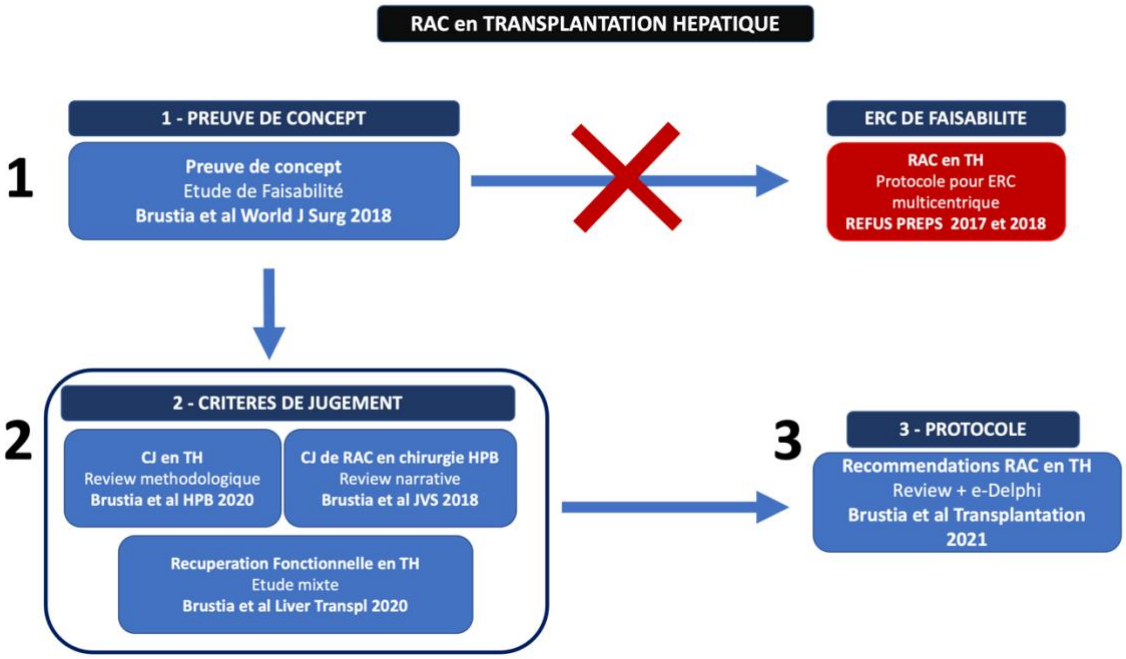


Figure 20. *Formalisation des recommandations sur RAC en TH.*

La troisième et dernière étape de ce travail de recherche est representée par la rédaction des recommandations sur **la RAC en TH,** fournissant une définition consensuelle et détaillée, pour permettre une homogénéisation des pratiques et incrémenter sa diffusion et reproductibilité. Cette étape a été fortement impulsée par la proposition directe de la Société ERAS, intéressée par l'ensemble des travaux portant sur le sujet jusqu'à présent.

Il a été décidé de rediger les recommendations sur la base de la litérature existante, sélon une révision systématique de la litérature, suivie d'un consensus de type e-delphi par un panel international d'experts[210].

La révision systématique de la littérature (PROSPERO CRD42019132798) se concentrait sur chacun des éléments RAC validés dans le domaine de la transplantation hépatique. Chaque élément a été défini par un groupe de mots-clés spécifiques extraits des recommandations officielles RAC et d'une étude pilote sur RAC et TH. Parmi les études incluses, 40 (93 %) étaient monocentriques, avec une médiane de 105 (38,5-171,5) patients. Le design était prospectif dans 25 (55,8 %) des études incluses, dont 12 (27,9 %) randomisées. L'intervention expérimentale était non pharmacologique, pharmacologique et combinée dans 23 (53,5 %), 19 (44,2 %) et 1

(2,3 %) des études. Le niveau de preuve rapporté selon le GRADE a été évalué comme élevé dans 3 (7 %), modéré dans 16 (37,2 %), faible dans 16 (37,2 %) et très faible dans 7 (16,3 %) des 43 références publiées. La révision a été suivie d'un consensus de type e-delphi sur chacun des 22 éléments de la RAC par un panel international d'experts en chirurgie et anesthésie de 12 centres de greffe internationaux, dont le comité de pilotage (Liège-Belgique, Sao Paulo-Brésil, Montréal-Canada, Turin-Italie, Pise-Italie, Kyoto-Japon, Groningue-Pays-Bas, Paris-France, Alicante-Espagne, Genève-Suisse, Portland-US, Edimbourg-Royaume-Uni). Nous avons prédéfini une séquence de type e-Delphi en trois tours. Le consensus était considéré comme atteint si plus de 80 % des experts notaient l'élément dans la région la plus élevée de l'échelle (7, 8 ou 9 sur l'échelle de Likert en 9 points). Une fois qu'un consensus était atteint pour un point donné, ce point était supprimé et n'était plus proposé au tour suivant. Parmi les 27 experts invités, 21 (81 %) ont répondu de 12 centres internationaux de TH avec un volume médian de 70 (40-112) TH par an. L'ensemble de ces éléments ont permis la rédaction de la première édition des recommandations. Cette revue systématique souligne à quel point les preuves disponibles actuellement pour formaliser un protocole de RAC en transplantation hépatique sont rares et manquent d'homogénéité. Le niveau de preuve le plus élevé (niveau 1 ou 2) était disponible pour 13 des 22 éléments. Alors que la valeur des protocoles RAC a maintenant été démontrée dans la chirurgie du foie, colorectale et du pancréas, montrant un avantage en termes de morbidité, de coût et de résultats médico-économiques, il est clairement nécessaire de réaliser des études de haute qualité pour confirmer l'avantage de la RAC en transplantation hépatique. (ANNEXE 5)

Brustia R, Monsel A, Skurzak S, Schiffer E, Carrier FM, Patrono D, Kaba A, Detry O, Malbouisson L, Andraus W, Vandenbroucke-Menu F, Biancofiore G, Kaido T, Compagnon P, Uemoto S, Rodriguez Laiz G, De Boer M, Orloff S, Melgar P, Buis C, Zeillemaker-Hoekstra M, Usher H, Reyntjen K, Baird E, Demartines N, Wigmore S, Scatton O. Guidelines for Perioperative Care for Liver Transplantation: Enhanced Recovery After Surgery (ERAS) Society Recommendations. Transplantation. 2021 May 6. doi: 10.1097/TP.0000000000003808. Epub ahead of print. PMID: 33966024.

5 CONCLUSIONS

La transplantation hépatique est un projet thérapeutique complexe impliquant un parcours de soins exigeant, qui pourrait bénéficier de l'application de la RAC pour minimiser la réponse au stress péri-opératoire.

Tout au long de ce travail de recherche, il a été mis en évidence que la RAC en TH est faisable et sûre, et que parmi les critères de jugement les plus pertinents, la durée de récupération fonctionnelle semblait la plus appropriée. L'originalité de cette récupération repose sur le fait qu'en transplantation elle s'applique au malade et au greffon, avec des critères pour chacun. De plus, en définissant la récupération fonctionnelle et donc l'indication médicale de sortie, nous avons mis en évidence une différence entre la sortie « médicalement autorisable » et la sortie effective. Ainsi, la différence entre ces deux dates permet d'étudier les freins à la sortie qui peuvent être de plusieurs ordres : culturels, sociaux, défauts d'organisation (manque d'organisation en aval, domicile, soins de suites…). La compréhension des freins à la sortie permettra d'améliorer ultérieurement la prise en charge de malades transplantés sur le plan médical, mais également sur le plan social et économique.

Il est évident qu'un programme d'une telle envergure ne peut pas reposer sur la bonne volonté d'une poignée de cliniciens. L'investissement sur des infirmièr(e)s de pratiques avancées (IPA), dédiés à l'application et au suivi d'un tel programme, pourrait contribuer à son succès. L'amélioration de la récupération après TH, la minimisation des complications, la réduction de la durée du séjour pourrait se traduire, comme pour la RAC en chirurgie colorectale, en un retour sur investissement à court terme.

Après la publication des recommandations sur RAC en TH et la définition de récupération fonctionnelle comme critère de jugement dédié, l'étape suivante reposera sur la promotion des recommandations, sur leur application, et une évaluation de l'implémentation à 1 et 3 ans. L'ensemble de ces éléments pourraient fournir des preuves de haut niveau scientifique pour permettre un réajustement des recommandations.

Ce travail de recherche a été remarqué par la communauté scientifique internationale : en collaboration avec l'International Liver Transplantation Society (ILTS), un groupe de travail multidisciplinaire (https://eras4olt.org/) composé, entre autres, d'anciens présidents de l'ILTS, de leaders dans le domaine de la transplantation hépatique et de jeunes cliniciens et scientifiques s'est donné l'objectif de diffuser le message de la RAC en TH. L'ensemble de ce travail de recherche sera présenté lors de l'introduction de la conférence de consensus à Valencia (Espagne) en janvier 2022. https://eras4olt.org/introduction.

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7 LISTE DES FIGURES

Figure 1. Représentation schématique des principales étapes du parcours d'un patient au cours d'une hospitalisation en vue d'une intervention chirurgicale.

Figure 2 : éléments d'un programme RAC générique

Figure 3 La courbe dose-réponse pour le remplissage vasculaire et les effets du déséquilibre. Adapté de Basic Concepts of Fluid and Electrolyte Therapy[22].

Figure 4 Aperçu d'un organigramme indiquant les différentes phases d'un protocole RAC générique, avec les rôles de chaque professionnel de santé impliqué pendant les des différentes phases du parcours de soins. PONV : Nausées et vomissements post-opératoires; IV intraveineux. Adapté de Ljungqvist et al[3].

Figure 5 Schéma du rapport entre la durée de récupération fonctionnelle (délai entre chirurgie et indication médicale de sortie) et durée de séjour hospitalier (délai entre chirurgie et sortie réelle). L'indication médicale de sortie (IMS) repose sur la satisfaction d'une liste de critères de récupération fonctionnelle.

Figure 6. Histogramme des principales indications de greffe. Données source extraites du rapport de l'ELTR de 2018[94].

Figure 7 Représentation schématique de la dissection des éléments pédiculaires, pendant la phase d'hépatectomie totale. D'après Sarr et al.[148]

Figure 8 Représentation schématique des plans de dissection en cas de (A) remplacement ou (B et C) préservation de la veine cave inférieure. D'après Sarr et al.[148]

Figure 9 Représentation schématique d'une transplantation avec remplacement de la veine cave inférieure (A) et préservation de la veine cave inférieure (B) avec anastomose en *Piggyback*. D'après Sarr et al.[148]

Figure 10 Exemple de hiérarchie du niveau de preuve[204].

Figure 11 Étapes de l'innovation chirurgicale.

Figure 12 résumant le projet d'étude randomisée contrôlée sur 3 centres comparant la RAC à une prise en charge standard en TH. R : randomisation, Rec. F : récupération fonctionnelle, IMS : indication médicale de sortie, S : sortie

Figure 13 résumant les principales étapes de la recherche, en rapport avec les 4 étapes du processus d'évaluation de l'innovation en chirurgie. RAC : récupération améliorée en chirurgie, TH : transplantation hépatique, CJ : critères de jugement, HPB : hépato-bilio-pancréatique, PREPS : programmes de recherche sur la performance du système de soins.

Figure 14 résumant les trois principales étapes de la recherche (preuve de concept, critères de jugement, recommandations), avec les publications correspondantes. RAC : récupération améliorée en chirurgie, TH : transplantation hépatique, CJ : critères de jugement, HPB : hépato-bilio-pancréatique, PREPS : programmes de recherche sur la performance du système de soins.

Figure 15. Preuve de concept

Figure 16 résumant les trois étapes pour la définition d'un critère de jugement de la RAC en TH. TH : transplantation hépatique, CJ : critères de jugement, HPB : hépato-bilio-pancréatique.

Figure 17. Première phase de l'analyse des critères de jugement : la greffe

Figure 18. Deuxième phase de l'analyse des critères de jugement : la RAC en chirurgie hépatique

Figure 19. Troisième phase de l'analyse des critères de jugement : définition de la récupération fonctionnelle en TH.

Figure 20. Formalisation des recommandations sur RAC en TH.

8 ANNEXES

8.1 ANNEXE 1

World J Surg
https://doi.org/10.1007/s00268-018-4747-y

ORIGINAL SCIENTIFIC REPORT

Enhanced Recovery in Liver Transplantation: A Feasibility Study

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Abstract

Background Enhanced Recovery After Surgery (ERAS) programmes after surgery are effective in reducing length of stay, functional recovery and complication rates in liver surgery (LS) with the indirect advantage of reducing hospitalisation costs. Preoperative comorbidities, challenging surgical procedures and complex post-operative management are the points that liver transplantation (LT) shares with LS. Nevertheless, there is little evidence regarding the feasibility and safety of ERAS programmes in LT.

Methods We designed a pilot, small-scale, feasibility study to assess the impact on hospital stay, protocol compliance and safety of an ERAS programme tailored for LT. The ERAS arm was compared with a 1:2 match paired control arm with similar characteristics. All patients with MELD <25 were included. A dedicated LT-tailored protocol was derived from publications on ERAS liver surgery.

Results Ten patients were included in the Fast-Trans arm. It was observed a 47% reduction of the total LOS, as compared to the control arm: 9.5 (9.0–10.5) days versus 18.0 (14.3–24.3) days, respectively, p <0.001. The protocol achieved 72.9% compliance. No differences were observed in terms of post-operative complications or readmission rates after discharge between the two arms. Overall, it was observed a reduction of length of stay in ICU and surgical ward in the Fast-Trans arm compared with the control arm.

Conclusion Considered the main points in common between LS and LT, this small-scale study suggests that the application of an ERAS programme tailored to the LT setting is feasible. Further testing will be appropriate to generalise these findings.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00268-018-4747-y) contains supplementary material, which is available to authorized users.

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Published online: 09 August 2018

Introduction

The Enhanced Recovery After Surgery (ERAS) programme is an evidence based, multimodal approach that aims to optimise perioperative management [1], to attenuate the response to surgical stress and improve recovery, decrease post-operative complications and hospital length of stay (LOS) [2, 3]. Major liver surgery is still affected by 3–5% mortality and 17–56% morbidity rate [4, 5], especially among frail patients: the management of pulmonary, renal and septic complications [4–6] including liver dysfunction require surgical, critical care and hepatology expertise, thus further complicating the patient's path. ERAS programmes are increasingly being applied to complex surgical procedures [7, 8], including liver surgery [9]: their implementation is associated with a 30–50% reduction in LOS, a 0.66 [95%IC:0.49–0.88] relative risk of perioperative complications, and reduced hospitalisation costs [10–14].

Preoperative comorbidities, challenging surgical procedures and complex post-operative management are the points that liver transplantation (LT) shares with liver surgery. Moreover, in Europe and Asia both the procedures are performed by the same hepato-pancreatic-biliary (HPB) surgical team. Considered a well-standardised and life-saving treatment for end-stage liver disease (ESLD) [15], LT remains an expensive and resource-intensive therapeutic intervention [16–18]: besides the surgical aspect [19, 20], ESLD complications [17] and post-operative immunosuppression [21] are responsible for 6–10% death rate within the first month [22] and 2–40% all-confounded morbidity [19–21, 23]. Although, in some selected cases, LT can be considered no more technically complex than major liver surgery, especially in low-MELD patients, with small HCC and compensated cirrhosis.

To date, some evidence exists on isolated items of ERAS programme tested on ESLD patients undergoing LT, as early extubation [24–26] or rapid recovery [27]. One single study recently reported the use of a 13-items enhanced recovery protocol in LT setting [28]. Despite, no firm conclusion can be driven on the basis of these publications.

Considered the main points in common between complex liver surgery and LT, including the same HPB surgical team, we decided to realise an adaptation, prospective small-scale *feasibility study* [29] focusing on the changing programme contents, to determine whether the use of an ERAS programme tailored to the LT setting, will be appropriate for further testing.

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Methods

Study design

The study was designed as a prospective single-arm, open-label, feasibility study of an ERAS programme adapted for LT (Fast-Trans programme).

The local Ethics Committee approved this study in July 2016 (ID RCB: 2016-A00676-45). All LT procedures were performed by the Liver Transplant Department, Hôpital Pitié-Salpêtrière, Paris, France.

All patients listed for LT underwent an extensive workup before their inscription, including oncologic staging in case of primary liver cancer, and among others cardiovascular, metabolic and nutritional status exploration. This latter was assessed either by measurement of the total psoas area at the 3rd lumbar vertebra [30] either through BMI [31]. Neither routine preoperative nutritional support [32, 33] nor adapted physical activity [34] is usually scheduled.

Patients were screened by one of the Authors (RB) in the outpatient consultation setting. If already on waiting list, patients were informed of the ongoing protocol and proposed to participate during the regular follow-up consultation. Alternatively, patients could be informed during the final outpatient consultation before subscribing to be listed, or during the pre-transplantation workup hospitalisation.

Reporting of this study followed the STROBE checklist for observational studies (supplementary material).

Study population (Fast-Trans arm)

Between August 2016 and May 2017, all patients receiving deceased-donor full-size grafts after circulatory death (DCD) or brain death (DBD), which matched the inclusion criteria, were eligible for enrolment in this study. In our institution, DCD grafts are considered exclusively in case of Maastricht III category (controlled cardiac arrest). All patients were informed of the study and gave their written consent to participate in it.

- Inclusion criteria
  Recipients participating in the study had to be 18 years old or older, with a MELD score <25 and provide their written informed consent before an organ was offered to them.

- Exclusion criteria
  Candidate recipients listed for multiple organ transplants, patients with fulminant liver failure, retransplantation, split or living donor LT, or MELD >26 were excluded from the study.
- Intraoperative exclusion criteria
  Complicated and technically demanding procedure from a surgical point of view.
  Blood transfusion >6 Red Blood Cell Units (RBC), indicative of a complex procedure.

Control population (control arm)

The Fast-Trans arm was compared with a match paired control arm having similar characteristics. To achieve a well-matched homogeneous control arm of adequate size, we included LT performed in 2015–2016 in the same centre and by the same team.

As for the Fast-Trans arm, were excluded recipients with a MELD score >26, cases of retransplantation, multi-organ transplantation, fulminant hepatic failure and split LT. Each patient in the Fast-Trans arm was matched retrospectively with two controls (1:2 ratio), based on a stepwise method (Fig. 1):

- Recipient's MELD score.
- Recipient's BMI $\pm$ 2 kg/m^2 (one recipient exception $\pm$ 6).
- Recipient's age $\pm$ 5 years (one recipient exception + 8/− 6).
- Recipient's gender.

Primary objective and endpoint

The primary objective of our study was to assess the impact of an ERAS programme in the LT setting on post-operative outcomes, evaluated from the total hospital stay.

Secondary objectives and endpoints

The secondary objectives of our study were:

- Clinical tolerance, evaluated in terms of the compliance with the items in the protocol.
- Post-operative outcomes, evaluated from the time to functional recovery, stays in the ICU, surgical ward and hepatology ward.
- Safety, assessed from the rates of readmission (0–30 days) after discharge, 90-day post-operative complications and 90-day mortality.

Procedures and protocol

No ERAS protocol goal-oriented specifically designed for LT is available in the literature. For this reason, we developed a modified protocol based on the evidence available on ERAS and liver surgery [9, 25, 35–39], which was specifically tailored for LT and its associated clinical pathway (Table 1).

Discharge criteria

Functional recovery was based on seven criteria that focused on both the patient and graft, defined as follows:

Patient-centred criteria:

- Adequate pain control with oral analgesics,
- Independently mobile,
- Tolerance of solid foods,
- No intravenous fluids.

Graft-centred criteria:

- Normal or declining levels of total bilirubin (TB), alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and a normal prothrombin time (PT) or at least 80% of the normal value,
- Good compliance with the immunosuppressive regimen, no immunosuppression-induced adverse effects (e.g., renal failure, tacrolimus overdose),
- Normal Doppler ultrasound findings.

When all of these seven criteria were met, we considered a patient to have functionally recovered. It is medically justified to discharge patients if they meet the criteria for a full functional recovery and are willing to go home [37].

Follow-up

No dedicated ERAS nurse coordination was available at the time of the study, and the adherence to the protocol was followed by two of the authors (RB and AM). After discharge, the liver transplantation coordination (four nurses specially trained and dedicated to LT) managed the follow-up schedule after the hospital discharge. A detailed list of outpatient consultation is offered to the LT patient, with a surgeon, a hepatologist and an anaesthetist. Before each consultation liver biology and liver echodoppler US is organised. During the first month after LT patients are seen every week, during the second month every 2 weeks, and later every month, for the first year.

The discharge was organised at home or care-home depending on familial, social and logistic environment of the patient.

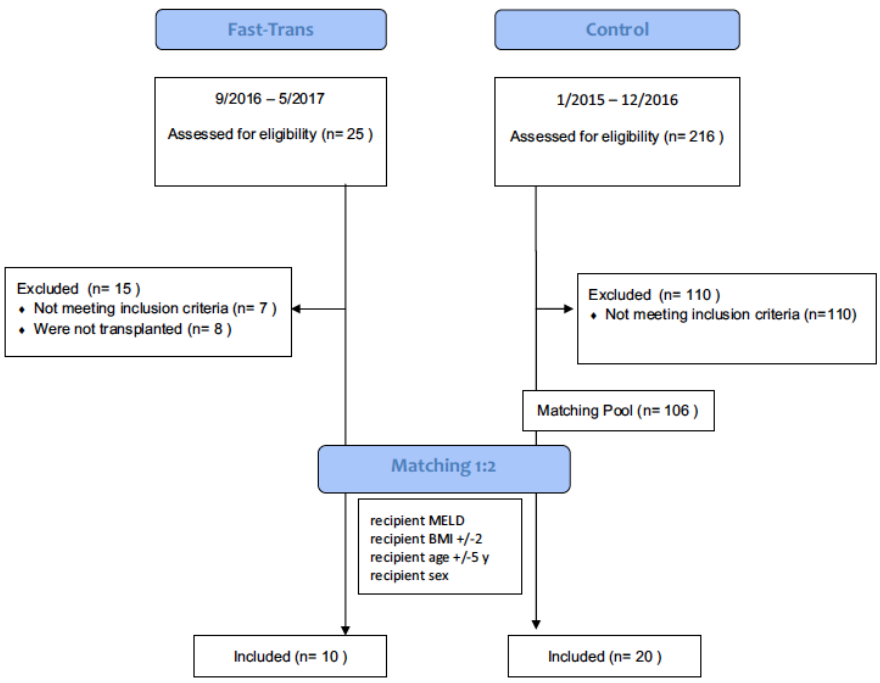

Fig. 1 Flow diagram of patient selection, and inclusion

Data collection and management

Baseline data (gender, age, body mass index, diabetes, underlying liver disease, presence of cancer and previous treatments) determined from the patient's medical history and physical examination, serum laboratory tests and appropriate preoperative workups were collected. Intraoperative data were also obtained on the donor (DCD/DBD, cause of death, graft weight, preservation solution) and recipient (duration of surgery, blood transfusion, cold ischaemia time, technical details on vascular anastomosis). Post-operative data (length of stay in the ICU and ward, complications) were also recorded, including compliance with each item of the protocol. Preoperative and intraoperative data were extracted directly at the end of LT or from the operative report and anaesthesiology monitoring report. Post-operative items were daily recorded in a dedicated form for each patient by two of the Authors (RB and AM): directly bedside or from digital ICU and ward records.

All data were collected in a prospectively maintained database dedicated to LT, declared to the *Commission Nationale de l'Informatiques et des Libertés* (French Data Protection Authority; CNIL No. 1929196).

In case of missing data in either the paper or digital files, the worst-case scenario data imputation was considered. In particular for functional recovery, given the retrospective nature of the control arm, the number of days from LT to discharge (LOS) were imputed to the number of days from LT to functional recovery, in the control arm.

Statistical analyses

The sample size calculation was based on primary outcome and endpoint (total hospital stay expressed in days). In our 2014–2015 LT cohort, the mean hospital stay of a subgroup of patients meeting the same inclusion criteria of this study was of 25 days ± 9. Based on the only study published in the literature observing a 36% reduction of the hospital stay in the experimental group [28], we expected a decrease of 35% in the Fast-Trans arm compared to the control arm. With a power of 80%, alpha error of 5%, and a 1:2 matching design, we calculated that 27 patients needed to be enrolled: 9 in the experimental arm and 18 in the control

Table 1 Experimental "Fast-Trans" protocol items

N	Preoperative	
1	Outpatient counselling and information	Regarding the procedure, recovery programme, discharge criteria and immunosuppressive regimen
2	Preoperative carbohydrate loading	Using a special high-carbohydrate drink. Because it is not possible to determine the exact timing of anaesthesia induction, the carbohydrate load is administered when the patient is admitted to the ward and waiting to go to the OR
3	Absence of pre-anaesthetic medication (anxiolytic)	Long-acting anxiolytic drugs are avoided
Intraoperative		
4	Antimicrobial prophylaxis and skin preparation	Intravenous antibiotics are administered before the skin incision and less than 1 h before LT. Post-operative "prophylactic" antibiotics are not recommended
5	Prevention of intraoperative hypothermia	Normothermia should be maintained during LT by means of a warmed IV fluids and an upper-lower body air-warming device
6	Incision	The choice of incision is at the surgeon's discretion; either an inverted L or J shaped incision. A Mercedes-type incision should be avoided because of the higher risk of incisional hernia
7	Adapted IV filling	Guided by trans-oesophageal intraoperative US, or using a Swan Ganz catheter
8	Temporary portocaval anastomosis	The use of a temporary PCS during OLT improves hemodynamic status, reduces intraoperative transfusion requirements, and preserves renal function during and after OLT
9	No prophylactic nasogastric intubation	Prophylactic nasogastric intubation increases the risk of pulmonary complications after hepatectomy. Its routine use is not indicated
10	No prophylactic abdominal drainage	The evidence available is not conclusive
11	Prevention of post-operative nausea and vomiting	A multimodal approach to PONV should be used. Patients should receive PONV prophylaxis with two anti-emetic drugs: ondansetron 4 mg IV and droperidol 0.625–1.25 mg IV
12	Antithrombotic prophylaxis and/or anti-aggregation	If PLT >50,000. Can be started intraoperatively if two arterial anastomoses or if the patient is considered to be at risk
13	Early extubation (<6 h after the end of LT)	According to extubation criteria
Post-operative		
14	Early mobilisation (POD1)	2 h at least on a chair, or four times a day
15	Patient-controlled analgesia	Morphine 5 mg/ml (150 mg in 30 ml). Patient-controlled dose: 1—3 mg. Lockout: 8–15 min. 4 h limit: 30–70 mg.
		PCA should be initiated after an initial bolus dose of 5–20 mg morphine (2–3 mg every 5 min up to 20 mg) to attain adequate plasma morphine concentrations. Doses should be reduced in patients aged over 70 years, and in those with severely compromised physical status
16	Gastric probe removal POD1	
17	Clear liquid per os POD1	
18	Enteral feeding per os POD1	Normal food intake should be started from day 1 after surgery
19	Stop IV fluids POD1	The central catheter is removed when leaving the ICU
20	*Per os* analgesia (POD2)	Nefopam: 20 mg/4—6 h
		Tramadol: 100 mg/12 h
		Morphine sulphate: 10 mg/4—6 h
21	Abdominal drain removal POD 2	If output less than 500 ml/day
22	Urinary probe removal POD2	
23	Stop IV analgesia POD3	
24	Independent mobilisation POD3	Can tolerate >6 h on a chair and/or walk three times a day
25	Daily revision of discharge criteria	When all eight are met, the patient is considered to have functionally recovered
26	Audit	

POD post-operative day, *IV* intravenous, *ICU* intensive care unit, *LT* liver transplantation, *PONV* post-operative nausea and vomiting

arm. Anticipating 10% dropout, 30 patients were enrolled in the study.

Categorical variables were reported in terms of percentages while continuous variables were summarised

using median and 25–75% values. Pearson's Chi-squared or Fisher's exact tests were used (as appropriate) for categorical variables and the Mann-U Whitney test for continuous variables. A p value <0.05 (two-tailed) was deemed to be significant. All analyses were performed using SPSS software, version 22.0 for Windows (SPSS Inc., Chicago, IL).

Results

Between September 2016 and May 2017, 76 LT was performed. Twenty-five patients were screened and included in the protocol, and 17 were transplanted: seven were subsequently excluded from the protocol and the remaining ten (13.1%) were considered for this analysis. These ten patients in the Fast-Trans arm were then matched 1:2 with 20 control patients who received standard care (Fig. 1). The matching variables (MELD, BMI, age and gender) were identical in both arms (Table 2).

Patient and donor characteristics

No differences were observed among the indications for LT in the two arms, except for a higher rate of Hepatocellular Carcinoma (HCC) (n = 9, 90% vs. n = 9, 45% respectively, p = 0.024), previous surgery (n = 9, 90% vs. n = 10, 50% respectively, p = 0.049) and an older donor age (78.8 (60.1–89.3) vs. 52.4 (46.0–83.6) years, respectively, p = 0.005) in the Fast-Trans arm than in the Control arm (Table 2).

Preoperative and intraoperative characteristics

The pre- and intraoperative characteristics of the patients are summarised in Table 2.

Some marked differences were observed between the two arms regarding specific elements of the protocol, such as preoperative information and carbohydrate drink loading, but only in the Fast-Trans arm. Patients in this arm were also extubated earlier (2.0 (0.0–2.0) versus 7.5 (4.5–13.0) hours respectively, p = 0.001), and fewer of them required an abdominal drain (n = 5, 50% vs. n = 19, 95%, respectively, p = 0.002) at the end of LT than in the control arm. No differences were observed in terms of the duration of surgery, cold ischaemia time or blood transfusions. No episodes of primary non-function (PNF) or early allograft dysfunction (EAD) were observed.

Post-operative characteristics

Patients in the Fast-Trans arm resumed *per os* analgesia (3 (1.0–4.0) vs. 4.5 (2.7–6.3) days, respectively, p = 0.017) and solid food intake (2 (1.0–2.0) vs. 4 (3.0–5.5) days, respectively, p = 0.000) sooner after surgery. Similarly, central venous catheters (2 days (2.0–5.0) vs. 6 days (4.5–7.8) respectively, p <0.001), gastric probes (0 (0.0–0.5) vs. 2 (1.0–4.3) days, respectively, p = 0.000), urinary probes (1 (1.0–2.5) vs. 6 (2.7–7.8) days, respectively, p = 0.000) and abdominal drains (1 (0.0–2.5) vs. 4 (2.0–5.3) days, respectively, p = 0.012) were also removed earlier than in the control arm (Table 3).

Primary outcome

In the Fast-Trans arm, it was observed a 47% reduction of the total length of stay, as compared to the control arm: 9.5 (9.0–10.5) days versus 18.0 (14.3–24.3) days, respectively, p <0.001 (Table 4).

Secondary outcome

- Overall, the observed compliance with the protocol was of 72.9% in the Fast-Trans arm (Fig. 2).
- The post-operative outcomes in the Fast-Trans arm versus the control arm, evaluated from the time to functional recovery, was of 7.5 (6.0–7.0) versus 18 (14.3–24.3) days (p <0.001), stays in the ICU 3 (2.0–4.0) versus 4.5 (3.0–8.3) days (p = 0.005) and surgical ward 1.5 (0.0–2.0) versus 6 (0.0–8.3) days (p = 0.01). In the hepatology ward, the time to functional recovery observed was of 6 (5.0–6.0) versus 7 (6.0–11.5) days (p = 0.53) (Table 4).
- No differences were observed in terms of post-operative complications (n = 5, 50% vs. n = 16, 80%, p = 0.08) and 30 days readmission rates after discharge (n = 3, 30% vs. n = 4, 20%, p = 0.07) (Table 4) in the Fast-Trans arm versus control, respectively. Post-operative mortality was nil in both arms.

Discussion

Enhanced Recovery After Surgery (ERAS) programmes are increasingly implemented in all fields of surgery, resulting in lower hospital stay, post-operative complications rate and hospitalisation costs [3, 13, 14, 40, 41].

LT is one of the more complex, expensive and resource-intensive therapeutic intervention that modern medicine has to offer [15, 16], and its considerable morbidity rate, heightens concern towards the financial climate of LT [16, 22]. Although in some selected case LT is no more complex than liver surgery, with short duration of surgical procedure, low transfusion rate, no abdominal drainage, early extubation and short hospital stay [8, 24–26, 42, 43].

Table 2 Patient and donors demography and preoperative characteristics

	Control	Fast-Trans	
Total $n = 30$	$n = 20$	$n = 10$	p
Male (%)	17 (85)	8 (80)	1
Age, Y	58.2 (52.6–65.3)	60.1 (52.5–66.1)	0.74
BMI (Kg/m^2)	23.6 (20.3–26.2)	24.6 (20.0–32.8)	0.85
BMI >35 (%)	2 (10)	1 (10)	1
ASA Score			1
2	13 (65)	7 (70)	
3	7 (35)	3 (30)	
MELD Score	7 (6–9)	7 (6–10)	0.81
Liver Disease (%)			
Alcohol	9 (45)	7 (70)	0.26
Viral cirrhosis	10 (50)	7 (70)	0.44
HBV	4 (20)	2 (20)	1
HCV	8 (40)	6 (60)	0.44
Metabolic syndrome	4 (20)	2 (20)	1
Biliary disease	3 (15)	0	0.53
HCC	9 (45)	9 (90)	0.024
Post-medical/surgical history (%)			
Tabagism	11 (55)	5 (50)	1
Ischaemic Heart disease	1 (5)	0	1
Previous surgery	10 (50)	9 (90)	0.049
Preoperative ascites	5 (25)	1 (10)	0.63
Donor characteristics			
Age, Y	52.4 (46.0–83.6)	78.8 (60.1–89.3)	0.005
BMI (Kg/m^2)	24.6 (21.1–32.0)	25.8 (22.7–34.7)	0.52
Graft detail			0.43
DBD	17 (85)	10 (100)	
DCD	2 (10)	0	
Domino	1 (5)	0	
Graft Weight (gr)	1405.0 (1080.0–1919.8)	1355.0 (934.5–2033.5)	0.78
Preservation solution			0.039
Celsior®	0	1 (10)	
IGL-1®	7 (35)	2 (20)	
Scot-15®	10 (50)	2 (20)	
Custodiol®	3 (15)	2 (20)	

Categorical variables are reported using percentages; continuous variables are summarised using median and 25–75% percentiles

BMI body mass index, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *MELD* model for end-stage liver disease, *HCC* hepatocellular carcinoma, *DBD* donation after brain death, *DCD* donation after cardiac death

Our centre performed every year more than 180 liver procedures, for primary liver cancer or liver metastasis [44–48], and the same HPB surgical team realise yearly more than 100 LT [49, 50].

Despite the malnutrition high prevalence in cirrhosis [17], ERAS recommendations for liver surgery are equally fit for these patients that may require an hepatectomy for liver cancer, later followed by LT. Sarcopenia, moreover, is the common negative point affecting outcomes in liver surgery and LT as well [17]. Nevertheless, given the main points in common between liver surgery and transplantation, including the same HPB surgical team, we decided to test the feasibility of a tailored ERAS programme on a small selected series of "easy" LT.

This being said, surgeons, intensivists and hepatologists showed some reluctance in changes such as the no-drain

Table 3 Preoperative and intraoperative characteristics

	Control	Fast-Trans	*p*
Total *n* = 30	*n* = 20	*n* = 10	
Preoperative information	0	10 (100)	0.001
Preoperative carbohydrates drink	0	5 (50)	0.002
Premedication	0	1 (10)	0.33
Balanced IV anaesthesia	20 (100)	10 (100)	NS
Hypothermic prevention	20 (100)	10 (100)	NS
Antibiotic therapy	20 (100)	10 (100)	NS
Surgical procedure			
Incision			0.078
Inverted J shaped	9 (45)	7 (70)	
Inverted L shaped	11 (55)	2 (20)	
Mercedes	0	1 (10)	
Ascites (ml)	0 (0.0–75.0)	0 (0.0–275.0)	0.95
Caval anastomosis			0.44
Piggyback	18 (90)	10 (100)	
Cava replacement	2 (10)	0	
Temporary portocaval anastomosis	17 (85)	10 (100)	0.53
Biliary anastomosis			0.54
Bilio-biliary anastomosis (%)	18 (90)	10 (100)	
Hepaticojejunostomy	2 (10)	0	
Biliary drainage			0.26
Internal	3 (15)	4 (40)	
Kehr	1 (5)	0	
Abdominal drain	19 (95)	5 (50)	0.002
Cold ischaemia (h)	6.1 (5.2–8.7)	6.6 (6.1–7.9)	0.62
Surgery duration (h)	6.7 (5.7–8.2)	6.0 (5.9–8.4)	0.21
Blood transfusion, patients	9 (45)	6 (60)	0.7
Blood transfusion, No. RBC	0 (0–4)	1 (0.5–3)	0.91
Intraoperative fluid filling	4000 (2875–4250)	4500 (3500–9250)	0.32
Early extubation <6 h (h)	7 (35)	9 (90)	0.007
Early extubation (h)	7.5 (4.5–13.0)	2.0 (0.0–2.0)	0.001
PONV	1 (5)	9 (90)	0.000

Categorical variables are reported using percentages; continuous variables are summarised using median and 25–75% percentiles

IV intravenous, *RBC* red blood cells, *PONV* post-operative nausea and vomiting

policy, rapid extubation and enteral feeding, as well as deperfusion and early mobilisation, despite published literature on focused elements of ERAS programme in LT.

Mandell and coll [26], showed—in 3 years—a 96% increase in the early extubation rate after LT, and triage directly to the surgical ward without ICU up to 82%, without compromising patient safety. Another study by Maffei et al. [51] showed that the introduction of an early intensive rehabilitation programme in the ICU after LT enabled patients to sit up sooner and resume intestinal transit earlier than patients in the control group.

All these studies focused on isolated elements of ERAS programmes: even if results are satisfactory, no single element but rather the combination of them in a structured protocol determines the outcome. [35, 52]. In this line, a different approach has been initiated by Rao and coll. [28], with a 13-points perioperative protocol in LT, with a significant reduction in ICU and total hospital stay in the experimental arm.

The principles of ERAS have been adopted by most specialties, producing their own specific protocols, with the generic pre-, intra- and post-operative elements adapted to some specialty specific and evidence-based interventions

Table 4 Post-operative characteristics, morbidity

	Control	Fast-Trans	*p*
Total *n* = 30	*n* = 20	*n* = 10	
Antiplatelet treatment	13 (65)	8 (80)	0.67
Opioid-based patient-controlled analgesia	1 (5)	2 (20)	0.251
Oral analgesia (pod)	4.5 (2.7–6.3)	3 (1.0–4.0)	0.017
Solid food (pod)	4 (3.0–5.5)	2 (1.0–2.0)	0.000
CVC removal (days)	6 (4.5–7.8)	2 (2.0–5.0)	0.000
Gastric probe removal (days)	2 (1.0–4.3)	0 (0.0–0.5)	0.000
Urinary probe removal (days)	6 (2.7–7.8)	1 (1.0–2.5)	0.000
Abdominal drain removal (days)	4 (2.0–5.3)	1 (0.0–2.5)	0.012
Hospital stay			
ICU (days)	4.5 (3.0–8.3)	3 (2.0–4.0)	0.005
Surgical ward (days)	6 (0.0–8.3)	1.5 (0.0–2.0)	0.01
Hepatology ward (days)	7 (6.0–11.5)	6 (5.0–6.0)	0.53
Time to functional recovery (days)	18 (14.3–24.3)	7.5 (6.0–7.0)	0.000
Total Length of stay (days)	18 (14.3–24.3)	9.5 (9.0–10.5)	0.000
Post-operative complications			
Clavien–Dindo			0.09
I	3 (15)	1 (10)	
II	11 (55)	4 (40)	
III	3 (15)	0	
Complications	16 (80)	5 (50)	0.08
Acute graft rejection	1 (5)	0	
Acute hyperglycaemia	1 (5)	0	
Acute renal failure	5 (25)	0	
Acute urinary retention	1 (5)	1 (10)	
Bile fistula	1 (5)	0	
Cardiac arrhythmia	1 (5)	0	
Confusion	1 (5)	0	
Early arterial stenosis	0	1 (10)	
Mild sepsis	3 (15)	0	
Nausea	0	1 (10)	
Peptic ulcer	1 (5)	0	
Surgical site haematoma	1 (5)	2 (20)	
Rehospitalisation <30d	4 (20)	3 (30)	0.07
Bile duct stenosis	2 (10)	1 (10)	
Impaired general condition	1 (5)	1 (10)	
Anaemia	1 (5)	0	
Haematuria	0	1 (10)	
Death	0	0	NS

Categorical variables are reported using percentages; continuous variables are summarised using median and 25–75% percentiles

POD post-operative day, *CVC* central venous catheter, *ICU* intensive care unit

[53]: in LT these are represented by the simultaneous care required by the complex interface between both patient and graft. Despite, the protocol of the aforementioned study by Rao and coll [28], lacks of specific interventions relevant for liver transplantation or graft care For this reason, and in the absence of stronger level of evidence a new, dedicated, multimodal protocol of care patient and graft centred relying on published data from liver surgery and transplantation, was designed. The same should be said for the detailed list of discharge criteria, involving both aspects of

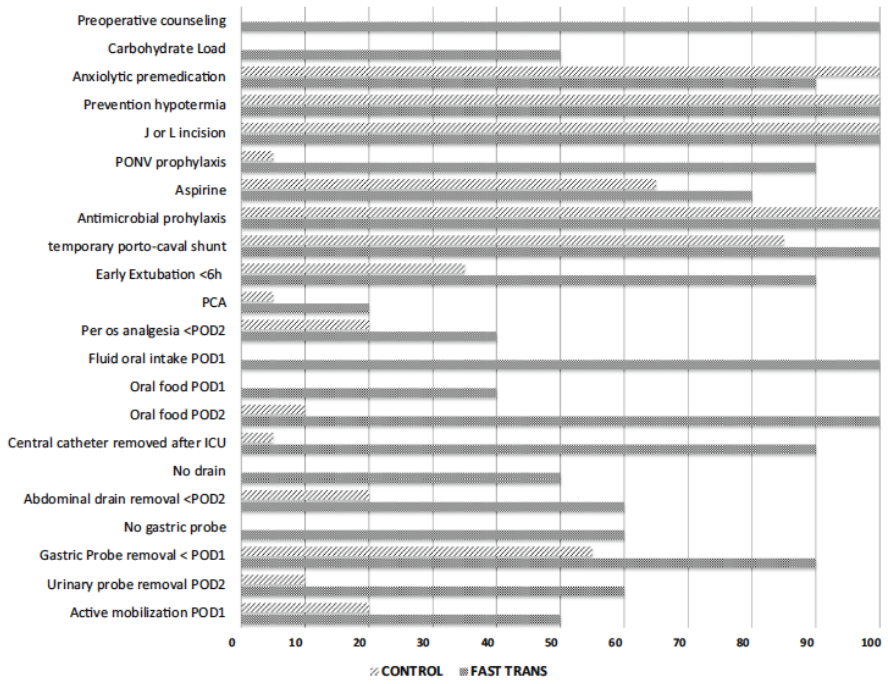

Fig. 2 Protocol items' compliance

treatment (patient-related and graft-related), to more precisely assess the "functional recovery" than simply borrow a checklist tailored for liver surgery [9].

In this way, we could observe a 47% reduction of the total length of stay in the experimental arm when compared to standard care. Only half of the patients in the experimental arm required an abdominal drain, and compared to the control arm, this was removed earlier. Extubation, CVC, gastric and urinary probe were removed earlier in the experimental group compared to the control one, as well. The compliance to the protocol items was as high as 72.9% (Fig. 2), comparable to that observed during previous ERAS programmes [40, 41]. Moreover, similar rates of early readmission and post-operative complications in both arms were observed in both groups: these results are even more interesting when considering the older donor's age and the higher rate of previous surgery in the Fast-Trans arm when compared to the control arm.

Interestingly, no difference in time of surgery nor in transfusion rate was observed in the two arms, supporting the idea that perioperative care, more than surgery in itself, is associated with better outcomes.

This study had several limitations: first, due to safety concerns, the inclusion and exclusion criteria for the Fast-Trans arm resulted in stringent selection. In particular, MELD score <25 and transfusion of less than 6 RBC units cut-offs, were decided after common discussions with the surgical and anaesthesiology medical staff, despite the existing literature [26], to minimise any risk towards patients. The counterpart is that patients involved represented no more than 10% of our yearly cohort. Moreover, we can understand that in centres where the HPB and transplant team are not the same, some concerns about feasibility of this approach could be argued.

Second, in the absence of a dedicated nurse coordinator, the ERAS protocol was led and monitored by surgeons and intensivists, and thus less efficiently than by a trained and dedicated coordinator.

Unlike digestive or pancreatic surgery [3, 7, 11], the effect-size of ERAS on the reduction of complications rate in liver surgery is little, and often limited to Clavien–Dindo grade I [10, 54, 55]. One of the reasons can be related to the considerable inherent morbidity of liver surgery, which is even higher in liver transplantation, given the ESLD

morbidity and the immunosuppressive regimen. Not surprisingly, no difference in complication rate was observed in this study, given the limited sample size and because the study was not designed for that purpose. Besides, the observed reduction in LoS can be explained by the active stimulation of patients since the end of LT, for bedside mobilisation, early feeding and drains removal in the experimental group. Finally, the single-centre design of this study precluded any further generalisation of our findings.

Conclusion

In conclusion, the specificity and innovative nature of our study were to focus on simultaneous care of the patient and liver graft: the largest part of the ERAS guidelines for liver surgery items could be transposed to the LT clinical pathway with a dedicated, *patient- and graft-centred* protocol and discharge checklist. Our data suggest that its application would be feasible, but the generalisation of these findings warrants further larger, prospective, randomised clinical trials using the same or a similar protocol, with broader patient's inclusion criteria.

Author contributions OS, OL, AM and RB conceived and wrote the manuscript. All Authors were in charge of patients, revised and approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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https://doi.org/10.1016/j.hpb.2019.12.010 HPB

REVIEW ARTICLE

A methodological review of clinical outcomes reported in liver transplantation trials

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Abstract

Background: Liver Transplantation (LT) is a life-saving treatment for end-stage liver disease, for which various outcomes are measured in randomized clinical trials (RCT). The aim of this methodological review is to evaluate and classify outcomes reported in RCT in LT.

Methods: PubMed and ClinicalTrials.gov were searched in July 2018 for published and ongoing RCTs on LT in the last 5 years. Studies were eligible if focusing on first LT in adult patients, with interventions during the perioperative period. Data extracted concerned LT characteristics, type of intervention, methodological characteristics and outcomes assessed.

Results: Of 2685 references, 55 were included with a median of 78 (40–120) patients for published trials and planned to include 117 (55–218) patients for ongoing trials. Morbidity was the most frequently used as primary outcome in 37 published (67%) and 13 ongoing trials (54%). We identified 10 different definitions for graft dysfunction, 9 for recovery outcomes and 12 different time-points for mortality. For published trials, among the 397 outcomes specified in the method section, results were reported for 283 (71%).

Conclusion: Outcomes reported in LT trials are very heterogeneous. A consensus approach to develop a core outcome set (COS) should be considered allowing for comparisons of results across trials.

Prospero: CRD42018108146.

Received 25 September 2019; accepted 15 December 2019

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Introduction

Liver Transplantation (LT) is a life-saving treatment for end-stage liver disease (ESLD).[1] Five decades after its introduction, more than 90 000 procedures have been performed in Europe,[2] with 1-year survival evolving from 64% to 66% in 1985 to 90%–92% in 2015 both in Europe[2–5] and the US.[6,7] Despite improved survival, LT remains associated with serious morbidity, ranging from 2 to 40% across series,[8–14] related to co-morbidities, surgical challenges,[11,12] infectious complications and postoperative immunosuppression.[9,11–13] This morbidity is responsible for a mortality rate of 6–10% within the first month,[2] with extra-hepatic organ failures being the major causes of morbidity and graft loss.

The evaluation of appropriate clinical outcome measures, including complications and other patient-centred outcomes, rather than surrogates is crucial in comparative effectiveness research to compare results across studies and combine them in meta-analyses. Unfortunately, the lack of standardisation of outcomes evaluated, as well as selective reporting of significant outcomes is very common, making data synthesis challenging.[15]

A possible solution to address these issues is the development and application of core outcome sets (COS), defined as an agreed minimum set of outcomes to be measured and reported in all studies of a specific condition.[15] COS development maximizes the usefulness of individual trials, by reducing heterogeneity in outcomes evaluated and allowing their combination in meta-

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analyses, thus increasing global research efficiency and reducing research waste.[15–17] The need for COS development was recently acknowledged in the field of complex surgery with COS being developed for colorectal,[18] bariatric,[19] oesophageal[20] and cardiac surgery,[21] as well as kidney transplantation.[22] To the best of our knowledge, no COS has yet been developed for liver transplantation.

The aim of this methodological review is to evaluate and classify short term outcomes (up to 1 year) reported in randomized clinical trials (RCTs) performed for adult LT, in order to inform COS development and provide recommendations for future study design.

Methods

We performed a methodological review of recently published and ongoing randomised controlled trials in liver transplantation. This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols (PRISMA-P) Statement.[23] The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 12th September 2018 (CRD42018108146).

Search strategy

We searched MEDLINE via PubMed for published trials via a multifaceted search equation using a combination of specific key-words and free-text words for liver transplantation, as well as the Cochrane filter to identify RCTs. Manual cross-referencing of the included studies was performed to identify relevant citations.

To focus on current practice and to ensure stability of survival rate, the search was limited to studies published during the last 5 years.

The search was conducted on 30/06/2018 and updated on 30/08/2018.

On 06/07/2018, we also searched for ongoing trials registered during the last 5 years at ClinicalTrials.gov with the following search terms: "liver transplantation" as condition, "interventional" as study type, "recruiting" as recruitment status, "phase 3", "phase 4" and "non applicable" as phase.

Eligibility criteria

Studies were selected using the following criteria:

Participants

We included studies on human adult patients (18 years or older) undergoing LT. Articles focussing on retransplantation or combined LT (with kidney, heart, lung, pancreas or intestine) were not considered because of different patterns of morbidity and mortality. Studies focusing on paediatric populations and experimental studies on cells, tissue or including animals were not considered for inclusion. Studies focusing on autotransplantation in cases of extreme liver surgery were also not considered for inclusion.

Interventions

No restriction on the type of intervention tested was considered, provided that the whole set of the target population included patients undergoing LT. The intervention could be performed before, during or immediately after LT (during the in-hospital period). Any intervention without a clear clinical relation to liver transplantation, not patient-centred or related to a non-relevant therapeutic outcome was not considered (e.g. bioequivalence or pharmacokinetic studies, pedagogic intervention on a simulated LT, or performance characteristics of two different monitoring strategies). Similarly, studies considering LT as an outcome measure was not considered (e.g. an intervention tested to avoid LT, using as an endpoint the time-to-LT or the number of LT-free patients).

Study design

We included only randomised clinical trials. Abstracts, letters to the editor and conference posters were not considered for inclusion because of the incomplete description of study methodology and results.

Setting

No restrictions on study location or settings were applied.

Follow-up

We considered studies reporting follow-up up to 1 year after LT for inclusion. Studies focusing on longer term outcomes were considered for inclusion only if data on short term outcomes up to 1 year were reported. Post-hoc analyses or long-term follow-up of previously published RCTs were not considered.

Language

We considered articles reported in English, French or Italian. Studies in other languages were included only if the translation could be accurately obtained through Google translate.

Selection process

The results of the literature search were uploaded to Rayyan, a web-based reference manager,[24] to facilitate the selection process.

The titles and abstracts identified by the search were reviewed by one author (RB) to select reports for full text evaluation based on eligibility criteria. In case of duplicate or overlapping reports, the article including the largest number of patients and reporting the primary outcome was included. Doubtful inclusions were resolved through discussion with a senior reviewer (AD).

Data extraction

A standardized data collection form, specifically designed with Google forms for the purpose of this study, was used for data extraction from published articles or for ongoing trials at ClinicalTrials.gov.

The following data were collected for each selected study:

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1 General characteristics: Study design, number of participating centers, total number of patients included for published trials, or expected sample size for ongoing trials at ClinicalTrials.gov, as well as the duration of the study. We assessed whether the authors clearly reported the presence of a funding source, as well as its private or public nature.
2 Liver transplantation characteristics: Indication for LT and the type of graft used (whole or split graft, deceased or living donor).
3 Intervention: Timing of intervention (preoperative, peri-operative or early postoperative-up to discharge), type of intervention (pharmacologic, non-pharmacologic or both) and whether the intervention belonged to one of the following categories
  1 Anaesthesiology
  2 Graft conditioning
  3 Surgical technique
  4 Intensive care
  5 Immunosuppressive regimen
  6 Postoperative recovery including rehabilitation
  7 Other
4 Methodological characteristics: The risk of bias for each included study, using the Risk of Bias tool developed by Cochrane.[25]
5 Outcomes assessed: All primary and secondary outcomes reported in the methods section, or in the section 'Outcomes measures' at ClinicalTrials.gov. Outcomes were extracted with the related definition, the time point and the severity score when provided. For published articles, we assessed the consistency between outcomes reported in the methods and result section.

Classification of outcomes

Outcomes were classified in the following categories[2,26–28]

1 **Mortality**
  1 *Short term mortality* defined as mortality within 90 days after LT.
  2 *Intermediate mortality* defined as mortality occurring up-to 1 year after LT.
2 **Liver graft dysfunction**
  1 *Graft loss*, defined as any medical or surgical condition requiring re-transplantation, such as primary graft dysfunction or non-function[29] and death.
  2 *Early allograft dysfunction*,[29,30] defined as the presence of one or more of the following: (1) bilirubin>10 mg/dL of post-operative day 7; (2) INR >1.6 on postoperative day 7; (3) aminotransferase level (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) >2000 IU/mL within the first 7 postoperative days.
  3 *Acute or chronic cellular rejection*, defined as the deterioration of allograft function with biopsy showing infiltration by T cells and other leukocytes, with evidence of ductular injury and endothelitis.[31]
  4 *Small for size syndrome*, defined as graft-recipient weight ratio (GRWRs) < 0.8%.[32]
3 **Morbidity.** All complications occurring up-to 1 year after LT reported in the included articles were examined:
  1 *Perioperative morbidity* (e.g., blood loss, blood transfusion, reperfusion syndrome after declamping, readmission in ICU, surgical re-intervention, radiological or surgical drainage requirement, surgical site infection, primary closure or negative wound pressure etc).
  2 *Biological morbidity* (e.g. end-procedure blood lactates, transaminase peak, bilirubin or prothrombin time at any time point, decreased glomerular filtration rate etc.)
  3 *Technical complications*
    1 Biliary complications (e.g. leakage, stenosis)
    2 Vascular complications (e.g. haemorrhage, thrombosis or stenosis)
  4 *Medical complications*
    1 Neurologic (e.g., peripheral neuropathy, psychosis, convulsions, tremors, neurotoxicity, hemiplegia, hallucination)
    2 Pulmonary (e.g., endotracheal re-intubation, pneumonia, pleural effusion, pneumothorax, pulmonary embolism)
    3 Cardiovascular (e.g., cardiac arrhythmia, coronary artery disease, myocardial infarction)
    4 Gastrointestinal (e.g., diarrhoea, constipation, abdominal discomfort)
    5 Renal (e.g., acute kidney injury, renal failure, renal replacement therapy and dialysis)
    6 Infectious (e.g., Sepsis, septic shock)
  5 *Primary disease recurrence*
  6 *Hospital readmission*
4 **Recovery outcomes**
  1 early (e.g. duration of LT and cold ischaemia time, time span from LT to extubation)[33,34]
  2 intermediate (e.g. length of stay in ICU, length of stay in hospital, time to functional recovery, etc.)[33,34]
5 **Patient reported outcomes** (PRO) such as pain, disability, fatigue and quality of life.

Statistical analysis

The statistical analysis was mainly descriptive. For continuous variables, we computed medians (quartile 1 [Q1] quartile 3 [Q3]), and for qualitative variables, frequencies (percentages). We described published and ongoing trials separately. Statistical analysis involved the use of R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria (http://www.R-project.org/).

Results

Among the 2685 references identified by the PubMed search, 55 were included. From the search on Clinicatrials.gov, we identified 67 references and included 24 ongoing trials. The

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selection process is detailed in Fig. 1, and the complete list of trials can be found in Supplementary_material_study_list.

Characteristics of the included trials

Among the included trials, 40 (73%) published and 15 (62%) ongoing were from single centres. Europe was the most frequent location of the trial's corresponding author (33% and 42% for published and ongoing trials, respectively). The trials included a median of 78 (40–120) patients for published trials and planned to include 117 (55–218) for ongoing trials. The experimental intervention was non-pharmacological in 20 published (36%) and 18 ongoing (75%) trials, and pharmacological in 35 published (64%) and in 6 ongoing trials (25%). The intervention was administered during the peri-operative period in 36 published (65%) and in 17 ongoing trials (71%).

Details on the type of graft used were provided by 27 published (49%) and 10 ongoing (42%) trials: cadaveric 13 published (24%) and 7 ongoing (29%) trials and LDLT in 19 published (35%) and 4 ongoing (17%) trials. More details are shown in Table 1.

The risk of bias for the 55 published trials is reported in Supplementary_Table 1. Briefly, the risk of bias for random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment and incomplete outcome data was rated as high in 22 (40%), 24 (44%), 29 (53%), 22 (40%) and 14 (25%) of trials, respectively.

Outcomes evaluated

Primary outcomes

All the included trials reported primary outcomes in the methods section. Among published trials, 43 (76%) defined a single primary outcome, 4 (7%) trials two primary outcomes, 7 (13%) trials three primary outcomes and 2 (4%) trials four primary outcomes. Similarly, 19 (79%) ongoing trials defined a single primary outcome, and 5 (21%) two primary outcomes (Table 2). Among the 55 published trials, 51 reported the results for the primary outcomes described in the methods (93%).

All outcomes

The median number of all outcomes defined in the methods section was 5.0 (3.0–7.0) in published and 4.0 (3.0–8.0) in ongoing trials (Table 3).

For published trials, among the 397 outcomes reported in the method section, 283 (71%) had results reported.

The network relationship of outcomes used in the same trial is represented in Fig. 2, as well as in the Supplementary_Table_2 (classification and timing of measured outcomes).

Mortality. Mortality was evaluated in 38 published (69%) and 13 ongoing (54%) trials: as primary outcome in one published (2%) and one ongoing (2%) trial; as secondary outcome in 37 published (67%) and 12 ongoing (50%) trials.

More than twelve different definitions were used, with the most frequent being "in hospital" for 9/36 (25%) published trials

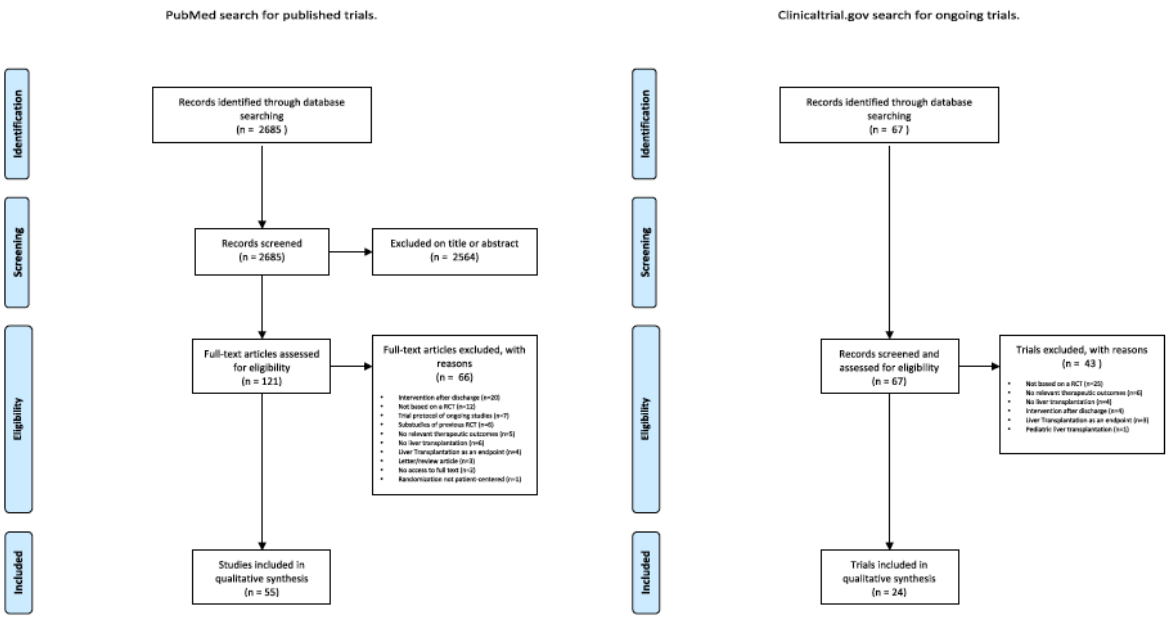

Figure 1 Flowchart selection of included published and ongoing studies

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Table 1 Characteristics of the selected trials

Characteristics	Published Trials n (%) N = 55	Ongoing Trials n (%) N = 24
Corresponding author location		
Europe	18 (33)	10 (42)
Asia	10 (18)	4 (17)
North America	7 (13)	5 (21)
Africa	4 (7)	3 (12)
South America	3 (5)	2 (8)
India	5 (9)	0 (0)
Australia	4 (7)	0 (0)
Middle east	4 (7)	0 (0)
Funding source		
Public	13 (24)	19 (79)
Not reported	18 (33)	0 (0)
Private	9 (16)	2 (8)
No funding	9 (16)	0 (0)
Private and public	6 (11)	1 (4)
Unclear	0 (0)	2 (8)
Patients enrolled (n)		
Median (Q1-Q3), range	78 (40–120), 10-893	117 (55–218), 24-500
Trial design, blinding		
Open label (unmasked)	20 (36)	12 (50)
Double blinding	22 (40)	8 (33)
Single blinding	11 (20)	4 (17)
Partially blinded	2 (4)	0 (0)
Trial design, centers		
Single center	40 (73)	15 (62)
Multicenter, National	7 (13)	7 (29)
Multicenter, International	8 (15)	2 (8)
Trial design, number of centers		
Median (Q1-Q3)	1.0 (1.0–2.5), 1-72	1.0 (1.0–4.8),1-15
Follow up, reported	42 (76)	22 (92)
Follow up, months		
Median (Q1-Q3), range	5.0 (1.5–9.5), 1-11	4.0 (1.8–8.0),1-36
LIVER TRANSPLANTATION CHARACTERISTICS		
Type of graft detailed	27 (49)	10 (42)
Cadaveric	13 (24)	7 (29)
LDLT	19 (35)	4 (17)
Details on Abdominal incision	3 (5)	Not applicable
Duration of surgery reported	26 (47)	Not applicable
Duration of cold ischemia reported	32 (58)	Not applicable
INTERVENTION		
Timing of intervention		
Peri-operative	36 (65)	17 (71)

(*continued on next page*)

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Table 1 (*continued*)

Characteristics	Published Trials n (%) N = 55	Ongoing Trials n (%) N = 24
Early postoperative	16 (29)	4 (17)
Preoperative	3 (5)	3 (12)
Class of intervention		
Anesthesiology/perioperative medicine	21 (38)	7 (29)
Graft_conditionning	9 (16)	6 (25)
Postoperative recovery including rehab'	8 (15)	4 (17)
Surgical technique	5 (9)	4 (17)
Immunosuppressive regimen	8 (15)	0 (0)
Other	1 (2)	3 (12)
Antifungal prophylaxis	2 (4)	0 (0)
Oncology	1 (2)	0 (0)
Intervention type		
Non Pharmacologic	20 (36)	18 (75)
Pharmacologic	35 (64)	6 (25)
Both	0 (0)	0 (0)

Q = quartile, LDLT = living donor living transplantation.

Table 2 Number and type of primary outcomes reported in the methods and results section of included trials

Characteristics	Published Trials n (%) = 55	Ongoing Trials n (%) = 24
Primary outcomes reported in the methods section *per* trial.		
Median (Q1-Q3), range	1.0 (1.0–1.0), 1-4	1.0 (1.0–1.0), 1-2
Single primary outcome	43 (76)	19 (79)
Two primary outcomes	4 (7)	5 (21)
Three primary outcomes	7 (13)	0 (0)
Four primary outcomes	2 (4)	0 (0)
Classification		
Morbidity	**37 (67)**	**13 (54)**
Perioperative	16 (29)	5 (21)
Biology	7 (13)	1 (4)
Medical	5 (9)	3 (12)
Technical	4 (7)	2 (8)
Other	2 (4)	2 (8)
Infectious	3 (5)	0 (0)
Graft dysfunction	**9 (16)**	**6 (25)**
EAD	4 (7)	5 (21)
Rejection	5 (9)	0 (0)
Graft loss	0 (0)	1 (4)
Recovery	**7 (13)**	**4 (17)**
Intermediate recovery	5 (9)	2 (8)
Early recovery	2 (4)	2 (8)
Mortality	**1 (2)**	**1 (4)**
Early mortality	1 (2)	1 (4)
Other	**1 (2)**	**0 (0)**
Feasibility	1 (2)	0 (0)
Primary outcome reported in result section	**51 (93)**	**Not applicable**

EAD = early allograft dysfunction Q = quartile.

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Table 3 Number and type of outcomes reported in the methods and results section of included trials

Characteristics	Published Trials n (%) = 55	Ongoing Trials n (%) = 24
Outcomes reported in the method section *per* trial.		
Median (Q1-Q3), range.	5.0 (3.0–7.0),2–13	4.0 (3.0–8.0),1–10
Outcomes reported in the method section, *total number*	**397**	**185**
Classification		
Morbidity	**52 (95)**	**20 (83)**
Perioperative	35 (67)	7 (35)
Medical complications	32 (62)	11 (55)
Biology	27 (52)	6 (30)
Technical	23 (44)	5 (25)
Infectious	23 (44)	1 (5)
Other	11 (21)	2 (10)
Graft dysfunction	**36 (65)**	**11 (46)**
Acute cellular humoral rejection	12 (33)	1 (9)
Early allograft dysfunction	9 (25)	4 (36)
Graft loss	8 (22)	4 (36)
Biopsy Proven Allograft Rejection	2 (6)	0 (0)
Small For Size Syndrome	2 (6)	0 (0)
Allograft dysfunction	1 (3)	0 (0)
Ischemia reperfusion injury	0 (0)	1 (9)
MEAF	0 (0)	1 (9)
Primary non function	1 (3)	0 (0)
Rejection	1 (3)	0 (0)
Mortality	**38 (69)**	**13 (54)**
Intermediate Mortality	16 (9)	9 (5)
Early mortality	7 (4)	6 (3)
Recovery	**31 (56)**	**12 (50)**
Length of stay, hospital	24 (77)	8 (67)
Length of stay, ICU	25 (81)	6 (50)
Time to extubation	13 (42)	0 (0)
Other	4 (13)	4 (33)
PRO	**7 (13)**	**4 (17)**
Symptoms	6 (11)	1 (4)
QoL	1 (2)	3 (12)
Outcomes reported in result section, *total number*	**283 (71)**	**Not applicable**

Y = yes, Q = quartile, EAD = early allograft dysfunction, ICU=intensive care unit, MEAF = model of early allograft function score, PRO = patient reported outcomes, qoL = Quality of life.

and both "3 months" or "one year" for 3/13 (23%) ongoing trials. The assessment of the time point for the outcome "mortality" was reported in 36 (65%) of published and 13 (93%) of ongoing trials.

Morbidity. Morbidity was assessed in 52 published (95%) and 20 ongoing trials (83%): as primary outcome in 37 published (67%) and 13 ongoing (54%) trials, and as secondary outcome in 18 published (18%) and 7 ongoing (29%) trials.

A severity score was assessed in 15/55 (27%) and 3/24 (12%) of published and ongoing trials, respectively. When looking at the most frequently reported morbidity classes, "peri-operative morbidity" was used as outcome in 35/52 (67%) published trials and "medical complications" in 11/20 (55%) ongoing trials.

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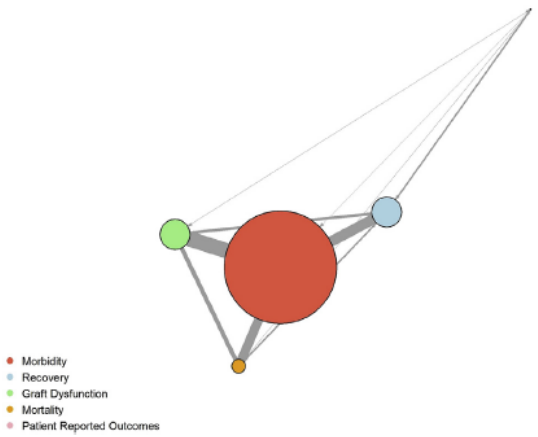

Figure 2 Network relations among outcomes reported in the same trial. The dot size is proportional to the rate of the outcome reported across all the included trials. The thickness of the line connecting the outcomes is proportional to the frequency of use of both outcomes in the same trial. As an example, the rate of trials reporting morbidity and graft dysfunction is higher than trials reporting morbidity and patient reported outcomes

More details on morbidity outcomes and classification are reported in Table 4 as well as in Fig. 3, this latter expressing the complex heterogeneity of morbidity classes and definitions.

Graft dysfunction. Graft dysfunction was assessed in 36 (65%) published and 11 (46%) ongoing trials: as primary outcome in 9 published (16%) and 6 ongoing (25%) trials, and as secondary outcome in 27 published (49%) and 5 ongoing (21%) trials.

Altogether, among the 72 (91%) trials assessing the graft dysfunction as an outcome, ten different definitions were reported. The most frequent used was "Acute cellular humoral rejection" for 12/36 (33%) published trials and both "Early allograft dysfunction" or "Graft loss" for 4/24 (36%) of ongoing trials. Similarly, nine different time-point were reported for graft dysfunction assessment, with "7 days" being the most frequent by both 7/36-assessed (19%) published and 5/11 (45%) ongoing trials.

More details in Supplementary Table 2.

Recovery outcomes. Recovery outcomes were assessed in 31 (56%) published and 12 (50%) ongoing trials: as primary outcome in 7 published (13%) and 4 ongoing (17%) trials, and as secondary outcome in 24 published (44%) and 8 ongoing (33%) trials.

More than nine different "recovery outcomes" were reported, with the most frequent being "Length of stay in ICU" in 25 (81%) published trials and "Length of stay in Hospital" in 8 (67%) ongoing trials.

Patient reported outcomes. Patient reported outcomes were assessed in 7 (13%) published and 4 (17%) ongoing trials, but never as primary outcome. When looking at the different PRO classes, "symptoms" were considered in 6 (11%) published trials and "Quality of Life" in 3 (12%) ongoing trials.

Intervention timing. A subgroup analysis of number and type of outcomes was realized merging the intervention variables "preoperative and perioperative" versus early postoperative.

Overall, 767 pre and perioperative versus 260 outcomes were measured within the included trials. Recovery or graft dysfunction outcomes were reported in 38 (14.6%) and 34 (13.1%) of trials focusing on postoperative interventions, compared to 38 (5.0%) and 37 (4.8%) in trials on pre and perioperative interventions, respectively (Supplementary Table 3).

Discussion

This methodological review of recently published and ongoing randomised clinical trials in liver transplantation found an important lack of standardisation of reported outcomes. Although morbidity and mortality were frequently considered, wide variation in the definitions used to describe the same outcome (e.g. 10 definitions for graft dysfunction, 9 for recovery outcomes), as well as heterogeneity in the timeframe of outcome assessment were evident (e.g. 12 different mortality time-points). We also found that patient-reported outcomes were very seldom reported and never as primary outcomes. Finally, we showed that some outcomes specified in the methods section were not reported in the results, suggesting a risk of selective outcome reporting.

Our results are consistent with previous methodological reviews conducted on other fields of surgery showing a lack of standardisation of outcomes and an overall poor quality of research. In a systematic review of 90 studies reporting the quality measurement of surgical wound infection, 41 definitions to define wound infection were identified.[35] More recently, a systematic review on 122 articles about outcomes after esophagectomy, reported ten different mortality measures across 115 studies, while definitions for at least one complication were given in only 27.6% of the studies.[36] This heterogeneity in outcome measures has important consequences as it prevents comparisons of results across studies and data synthesis in meta-analyses. This could be particularly true for mortality or recovery outcomes, for which the timing measure is more relevant than definition in itself.

Another problem is related to selective outcome reporting. We cannot exclude a risk of selective outcome reporting, as 7% of published trials did not report the results for the primary outcome and 29% of all outcomes (both primary and secondary) were not reported in the result section. This may also have a major impact on interpretation of results. Meta-research on 283 reviews regarding the impact of outcome reporting, found that

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Table 4 Detail of morbidity outcomes assessed and reported among the included trials

	N	Published Trials n (%) = 55 (70)	Ongoing Trials n (%) = 24 (30)
MORBIDITY			
Morbidity_assessed	79	52 (95)	20 (83)
Morbidity_perioperative	72	35 (67)	7 (35)
Blood_transfusion	42	15 (43)	2 (29)
Blood_loss	42	15 (43)	1 (14)
Surgical_reintervention	42	12 (34)	0 (0)
SSI	42	5 (14)	2 (29)
Reperfusion_syndrome	42	2 (6)	2 (29)
Readmission to ICU	42	2 (6)	0 (0)
Drainage	42	1 (3)	0 (0)
Biology outcomes	72	27 (52)	6 (30)
Transaminases_peak	33	16 (59)	5 (83)
Total Bilirubine_peak	33	18 (67)	1 (17)
Prothrombine time	33	9 (33)	0 (0)
Creatinine	33	8 (30)	0 (0)
Metabolites_tacro	33	7 (26)	1 (17)
Lactates	33	5 (19)	1 (17)
GFR	33	6 (22)	0 (0)
Hb	33	2 (7)	0 (0)
Complications_Technical	72	23 (44)	5 (25)
Biliary	28	15 (65)	5 (100)
Arterial	28	12 (52)	0 (0)
Hemorragic	28	7 (30)	0 (0)
Portal	28	6 (26)	0 (0)
Cava	28	2 (9)	0 (0)
Complications_Medical	72	32 (62)	11 (55)
Renal	43	23 (81)	5 (45)
Cardiological	43	12 (38)	3 (27)
Pulmonary	43	13 (41)	1 (9)
Neurological	43	10 (31)	1 (9)
Gastro_Intestinal	43	5 (16)	2 (18)
Endocrine	43	2 (6)	3 (27)
Hematological	43	1 (3)	0 (0)
Complications_Infectious	72	23 (44)	1 (5)
Bacterial	19	12 (67)	0 (0)
Viral	19	8 (44)	0 (0)
Fungal	19	7 (39)	0 (0)
Not_Stated	19	4 (22)	1 (100)
Disease_Recurrence	10	7 (78)	1 (100)
Hospital_Readmission	10	2 (22)	0 (0)
Severity_Reporting	74	10 (18)	3 (16)
Dindo_Clavien	8	5 (83)	0 (0)
CCI	8	0 (0)	1 (50)
NCCI_adv_events	8	1 (17)	0 (0)
MEAF	8	0 (0)	1 (50)

SSI=surgical site infection, ICU=Intensive care Unit, GFR = glomerular filtration rate, CCI = complication comprehensive index, MEAF = model of early allograft function score.

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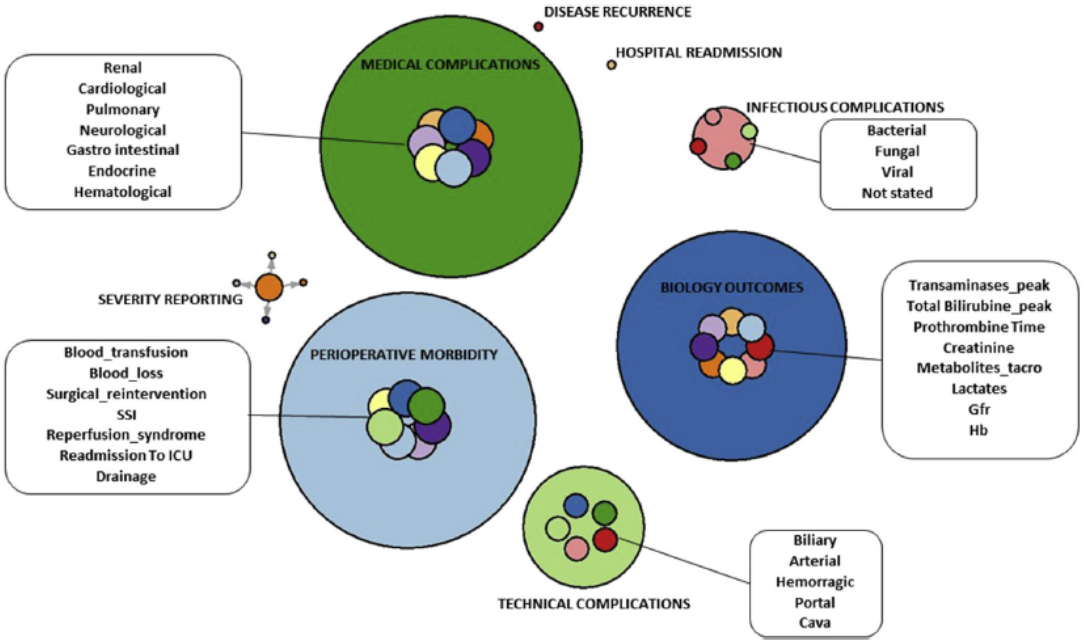

Figure 3 The figure details the heterogeneity among morbidity classes and definitions reported across the included trials. The size of the eight main dots (corresponding to the classes of morbidity) are proportional to the number of trials reporting the morbidity classes. Inner dots represent the definitions used for each morbidity class (SSI=Surgical Site Infection, ICU=Intensive Care Unit, GFR = Glomerular Filtration Rate, CCI = complication comprehensive index, MEAF = Model of Early Allograft Function score)

among 42 meta-analyses with a statistically significant result, eight (19%) became non-significant after adjustment for outcome reporting bias and 11 (26%) would have overestimated the treatment effect by 20% or more.[37]

An increasingly attractive solution to improve outcome reporting is to develop and popularise the use of a "core outcome set" (COS). A core outcome set is an agreed minimum set of endpoints that have to be measured and reported in all studies of a given disease.[38] This allows cross-study comparisons, reduces heterogeneity and increases the ability to perform data synthesis for the core set of outcomes. Investigators may of course add any outcome of particular interest to their study in addition to outcomes included in the COS,[36] and should be considered free to choose the most relevant outcome of interest (or time point), if none of the outcomes included in a given COS is adapted to the specific purpose of a trial. The COMET (Core Outcome Measures in Effectiveness Trials) initiative aims to collate and stimulate the development and application of COS. The initiative developed an online tool for presenting information on methodological reviews conducted and COS elaborated[15] with filters (general settings, health area, target population, methods, stakeholders involved, study type and publication year) to improve the efficiency of the search. A recent systematic review reported the development of 227 COS in the last three decades, with a wide range of disease categories including cancer, gastroenterology, rheumatology, anaesthesia but also intensive care and rehabilitation.[15]

There is no established COS for liver transplantation and this methodological review aims to be the base on which the COS developing process is built. Patient point of view is increasingly considered in COS development. In this study we found that only five trials (6.3%) had considered patient-reported outcomes, which is very low. Nonetheless, among them one was published and four are ongoing, suggesting a slight increase of researchers' awareness of this class of outcomes over time. Patient-important, patient-centred or patient-reported outcomes are increasingly considered as primary outcomes in many health domains, including cardiovascular disease, cancer, gastroenterology and surgery.[39] The measure of outcomes meaningful to patients is a cornerstone of comparative effectiveness research. This gives clinicians the ability to make better decisions by providing evidence on the effectiveness, benefits, and disadvantages of different treatments.[39]

We plan to organize an international working-group of experts, to develop a core outcome set, consisting of all relevant LT stakeholders (e.g. surgeons, hepatologists, anaesthetists, intensivists, and patients) to ensure that the COS is useful to evaluate this particular field of surgery and inform practice, as well as account for patient point of view. We will propose that a core outcome set for LT include at least one measure of each category reported, namely morbidity,

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graft dysfunction, mortality, recovery and patient-reported outcomes. Of course these measures may not be appropriated for all issues that researches wish to explore: for this reason, COS are intended to be complementary, and not a replacement of any of the outcome measure decided by investigators.

Besides the outcome reporting, this study offers a detailed picture on the recent panorama of trials in LT: the large majority are single center, with some national and even less international multicentre trials. This probably reflects logistical and methodological barriers of multicentre studies, not only in outcome reporting but in standardisation of preoperative and procedural variables across centers.

This review has several limitations. Firstly, the search was limited to studies published after 2014 and it is possible that trends in defining outcomes may have changed over the preceding years. Secondly, we decided to focus only on randomised clinical trials which are supposed to provide the highest level of evidence. The largest volume of published literature in the LT domain relies on cohorts or clinical series. It is possible that, had these other studies been included, the rate of each outcome class would have changed.

Conclusion

This study highlights the lack of standardisation in outcomes reported in liver transplantation trials, as well as the low consideration of patient-reported outcomes. This has important consequences as it may prevent comparison across studies and data synthesis in meta-analyses. The need to develop a core set of outcomes for liver transplantation is urgent and should include patient-reported outcomes. Researchers should be compelled to measure and report the core outcome set as a minimum for all studies in this condition.

Acknowledgements

We would like to thank dr Stefan Hofmeyr for English reviewing of this article. We wish to thank the Reviewers and the Editor for their constructive comments, which helped improve the article upon revision.

Conflicts of interest

None to declared.

Financial support

The present study is part of an ungranted PhD project on enhanced recovery after liver transplantation.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2019.12.010.

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8.3 ANNEXE 3

Journal of Visceral Surgery (2018) xxx, xxx–xxx

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REVIEW

Enhanced recovery after liver surgery

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KEYWORDS
Liver surgery;
Hepatectomy;
Enhanced recovery after surgery;
Systematic review

Summary

Introduction: In a majority of cases, enhanced recovery after surgery program (ERP) leads to a reduced rate of postoperative complications and shortened hospital stays following digestive surgery. The program's preoperative, perioperative and postoperative measures are implemented by the members of a motivated multidisciplinary team. Having shown its merits in digestive surgery, ERP would be particularly useful in liver surgery due to the elevated rates of morbidity and mortality this type of operation continues to entail. The objective of this review was to evaluate the efficacy of ERP in liver surgery.

Method: This is a systematic narrative review of the literature on the efficacy of ERP in liver surgery by laparotomy or laparoscopy.

Results: Notwithstanding a number of studies ($n = 30$: 5 randomized trials, 14 cohort studies and 11 meta-analyses) less sizable than with regard to digestive surgery in general and colorectal surgery in particular, analysis of the literature confirms that in liver surgery, ERP is associated with an overall decrease in complications by 30 to 60%, but without improvement in the rates of hospital readmission and postoperative mortality. All of the studies report a reduction in average length of stay (ALOS) by 2.3 days and in functional recovery, a more objective indicator than ALOS, by 2.5 days. As of now, the economic impact of the ERP programs in liver surgery is neither positive nor negative, the above-mentioned savings being counterbalanced by heightened costs for material and equipment. Laparoscopic surgery is independently associated with better outcomes in terms of complications, functional recovery and ALOS; that is why it is important to incorporate this surgical approach in ERP as often as possible. Given a lack of robust evidence, Prehabilitation, which is a preoperative optimization process leading to improved functional reserve, has yet to be assigned a place in ERP programs pertaining to liver surgery. Possible roadblocks to application of an ERP program can be overcome through coordination by a team leader, a motivated multidisciplinary team, training courses and dedicated teaching sessions.

Conclusion: ERP is a care improvement process that has a major play to play in organization of liver surgery, and its large-scale application is to be recommended.

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https://doi.org/10.1016/j.jviscsurg.2018.10.007
1878-7886/© 2018 Published by Elsevier Masson SAS.

Please cite this article in press as: Brustia R, et al. Enhanced recovery after hepatic surgery. Journal of Visceral Surgery (2018), https://doi.org/10.1016/j.jviscsurg.2018.10.007

Key points

- The objective of ERP is to decrease complication rates and to improve recovery. Its application in liver surgery is premised on a goodlevel of evidence.
- Implementation of an ERP program in liver surgery is associated with a decrease in morbidity ranging from 30 to 60%, and with a readmission rate similar to what has been observed in conventional management.
- Duration of hospital stay can be reduced by a mean 2.3 days, and functional recovery time by a mean 2.5 days.
- Laparoscopy should be preferred whenever possible.
- The rare published medico-economic studies have shown that ERP in liver surgery has no significant impact on costs.

Introduction

The concept of *Fast Track* or *Enhanced Recovery programme After Surgery* (ERP) was first introduced in the 1990s by H. Khelet and his colorectal surgery team, its objectives being to reduce the rate of postoperative complications and to shorten hospital stays [1]. Wishing to achieve decreased response to surgical stress and improved recovery, the program is built around a coherent sequence of preoperative, perioperative and postoperative measures based on scientific data in the literature. No single element is liable to improve surgical outcome; the key to success consists in synergy and in the sequencing of the phases of the program, one after another in the right order [1,2]. And if the program is to function effectively, with durably sound results, it behooves the multidisciplinary team working with a patient to possess complete and comprehensive vision of the care pathway and outcomes, with periodic readjustments brought on by regularly programmed audits [1,2].

For over 10 years and following publication of more than 580 studies, application of this type of program in digestive surgery has yielded a significant decrease in complication rates, more rapid functional recovery and less protracted hospital stays without heightened readmission rates [3]. Some of the reasons for improved quality of care are: the introduction of mini-invasive surgical approaches, deeper understanding of surgical stress, and optimized anesthetic care [1—3].

Since the publication of ERP recommendations for colorectal surgery, dedicated protocols for pancreatic (2012), urological (2013), gastric (2014), major gynecological (2015) and bariatric surgery (2016) have followed [1]. On the same token, several learned societies, including the French-speaking http://www.grace-asso.fr, have published recommendations specific to liver surgery; the main outlines are summarized in Table 1.

Wishing to achieve an overall synthetic vision of the results of ERP in hepatobiliary surgery, we have carried out a systematic review of the literature.

Method

In accordance with the PRISMA recommendations [6], the Pubmed and Pubmed Central data bases have been interrogated with regard to all the studies carried out over the past 10 years (2008—2018) with the following keywords: ''liver surgery'' and ''enhanced recovery after surgery''. Research activities carried out during February 2018 were updated in March 2018 (Flow chart; Fig. 1). Among the studies indexed ($n = 1009$) subsequent to elimination of duplicates and studies deemed not relevant on the basis of the title and the abstract; 5 randomized studies; 14 cohort studies (results in Table 2) and 11 meta-analyses (results in Table 3) were included.

Why ERAS in liver surgery?

Notwithstanding improved surgical techniques, as well as laparoscopic approach and anesthetic care [37], liver surgery remains a major operation with mortality ranging from 3 to 5% and postoperative morbidity from 17 to 56%, particularly in patients suffering from sarcopenia and/or underlying hepatopathy [38].

Possible pulmonary, renal or septic complications [38,39], or hepatic insufficiency can lead to longer hospitalization, additional health care (medication, laboratory or imaging examinations, re-do surgery) and increased risk of mortality at 30 days (HR = 2.96, 95% CI 1.07—8.17) [40]. All of these consequences have a direct impact on health costs.

From an oncological standpoint, complications following liver surgery (metastases, hepatocellular carcinoma...) are associated with reduced overall and disease-free survival. The activation of pro-inflammatory mediators responsible for impairment of immune response to cancer is one explanation for this phenomenon, as is delayed access to adjuvant treatment [39,41].

And yet, it is possible to implement and develop an ERP after this type of major surgery. The development of a laparoscopic approach, comprehension of the surgical stress associated with hepatic resection and optimized anesthetic care could help to minimize postoperative complications [1].

As is the case in other surgical areas, while a decrease in general complications following application of an ERP is to be expected, this does not hold true for the complications ''specific'' to liver surgery.

The particularities of ERP in liver surgery

For each protocol — and the liver is no exception to the rule — there exists a common and constant base, represented by a number of generic elements throughout the care pathway [1,42]:

- preoperative (informative consultation, reduced preoperative fasting, antibiotic or antithrombotic prophylaxis, no anxiolytic premedication);
- perioperative (short-acting anesthetic agents, suitable vascular filling, prevention of hypothermia, laparoscopic approach when medical expertise is available);
- postoperative (no gastric tube, systematic prevention of nausea and vomiting, early mobilization and refeeding, regularly programmed audits).

That much said, other elements have been added to the protocols dedicated to each specialty. Indeed, recommendations for ERP in liver surgery have incorporated the following specific elements [4,5]:

- preoperative:
  - preoperative nutrition for undernourished patients. Malnutrition is a recognized reversible risk factor for complications in liver surgery. At-risk patients (weight

Table 1 Summary of the ERP recommendations in liver surgery.

n	Element	Summary	Level of evidence	Degree of recommendation
1	Preoperative consultation	The patient should have a systematic dedicated consultation and targeted education before hepatectomy	Moderate	High
2	Preoperative nutrition	At-risk patients (weight loss > 10–15%, severe malnutrition BMI < 18.5 Kg/m^2, Albuminemia < 30 g/L) should receive nutritional correction 7 days before surgery (which can be put off for 15 days)	High	High
3	Immunonutrition	Limited evidence	Low	Low
4	Reduced preoperative fast	Preoperative fast not exceeding 6 h for solids and 2 h for liquids	Moderate	High
		Dedicated carbohydrate solution 2 h before induction to be proposed	Low	Low
5	Oral bowel preparation	Bowel preparation is not indicated	Low	Low
6	No anxiolytic premedication	Long-acting anxiolytic premedication is to be avoided. Anxiolytics with short half-life are to be preferred to anesthetic induction	Moderate	High
7	Antithrombotic prophylaxis	Low-molecular-weight heparin, 2–12 h before surgery	Moderate	High
		Intermittent pneumatic compression of the lower limbs during hepatectomy	Low	Low
8	Preoperative steroids	Metilprednysolone can be used before hepatectomy on healthy parenchyma to reduce intraoperative stress, without increasing risk of complications. To be avoided in diabetics	Moderate	Low
9	Antibiotic prophylaxis and skin preparation	Intravenous antibiotic therapy 1 h before incision (one dose)	Moderate	High
		Prophylactic postoperative antibiotic therapy not recommended		
		Detersive skin cleaning with Chlorhexidine 2% superior to iodine solution	Moderate	High
10	Incision	No recommendations. Mercedes incision to be avoided (risk of eventration)	Moderate	High
11	Mini-invasive approach	Laparoscopic surgery can be carried out by trained teams, particularly left lobectomy or resections of anterior segments	Moderate	High
12	Feeding tube (FT)	Systematic FT use increases the risk of pulmonary complications after hepatectomy	High	High
13	Systematic abdominal drainage	There exists no scientific proof for or against systematic abdominal drainage after hepatectomy	Low	Low
14	Prevention of hypothermia	Normothermia must be maintained during the hepatectomy	Moderate	High
15	Nutrition	A light meal (drink, dessert) is authorized from D1. Parenteral nutrition only in case of malnutrition or prolonged ileus (> 5D)	Early refeeding = moderate	High
			Dietary supplements = moderate	Low
			No systematic postoperative parenteral nutrition = high	High

Table 1 (*Continued*)

n	Element	Summary	Level of evidence	Degree of recommendation
16	Postoperative glucose control	Insulin treatment to maintain normoglycemia	Moderate	High
17	Prevention of gastroparesia	Greater omentum flap on left hepatectomy surface	High	High
18	Stimulation of intestinal transit	No indication	High	High
19	Early mobilization	Must be encouraged the day after the operation	Low	Low
20	Analgesia	No systematic indication of epidural anesthesia for open hepatectomies. An intrathecal infusion and a cicatricial catheter are possible alternatives	Moderate	High
21	Systematic prevention of postoperative nausea and vomiting	Multimodal approach = intravenous administration of two anti-emetic molecules	Moderate	High
22	Vascular filling	Maintenance of central venous pressure < 5 cm H_2O is recommended, and balanced crystalloids are to be preferred to saline solutions or colloids	Moderate	High
23	Audit	Regularly programmed audits increase team adhesion and improve results	Moderate	High

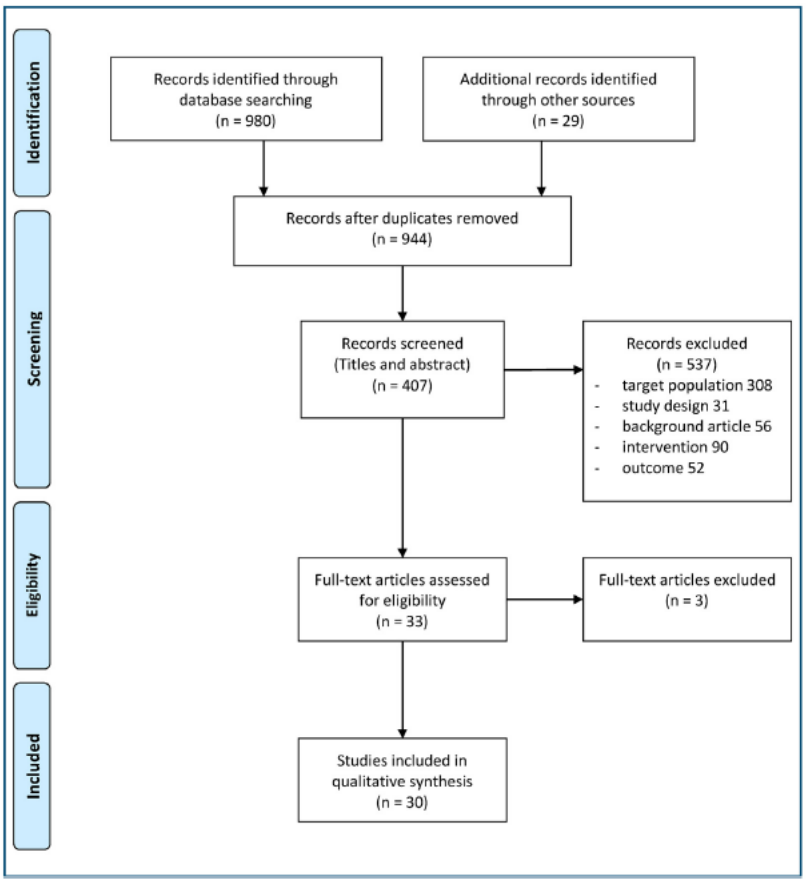

Fig. 1. Research strategy, selection of studies.

Table 2 Cohort studies and randomized trials.

Author	Year	Study	Comparison	Patients	Lap/Open	Morbidity (%)	Mortality (%)	ALOS (days)	Functional recovery (days)	Cost effectiveness
van Dam [7]	2008	Cohort	ERP vs. control	161	O	31 vs. 41	0 vs. 2	[a] 6 vs. 8		
Stoot [8]	2009	Cohort	ERP vs. control (Lap.)	26	L	1 vs. 1	0	5 vs. 7	[a] 3 vs. 5	
Sanchez-Perez [9]	2012	Cohort	ERPvs. control	43	L	12 vs. 12	0	2 vs. 3		
Schultz [10]	2012	Cohort	ERP (descriptive)	100	L-O	25	0	2 lap—5 *ouverte*		
Jones [11]	2013	RCT	ERPvs. control	91	L	15 vs. 11	2 vs. 2	[a] 4 vs. 7	[a] 3 vs. 6	
Dunne [12]	2014	Cohort	Initial vs. delayed ERP	304	L	38 vs. 38		6 vs. 6		
Dasari [13]	2015	Cohort	ERP vs. control	184	L-O	34 vs. 33	1 vs. 1	6 vs. 6	5 vs. 5	
He [14]	2015	RCT	ERP vs. control	86	L	15 vs. 16	0 vs. 0	[a] 6 vs. 10		[a] 7742yen ERAS vs. 9470yen control
Savikko [15]	2015	Cohort	ERP vs. control	134	L-O	[a] 37 vs. 71	0	[a] 4 vs. 6		
Hughes [16]	2016	Cohort	ERP (descriptive)	603	L-O	34	1.5	7		
Joliat [17]	2016	Cohort	ERP vs. control	174	L-O	[a] 49 vs. 64	1 vs. 2	[a] 8 vs. 10		42,356€ ERAS vs. 38,726€ control
Liang [18]	2016	RCT	ERP vs. control (Lap.)	187	L	[a] 33 vs. 44	0	[a] 6 vs. 10	[a] 5 vs. 8	
Page [19]	2016	Cohort	ERP vs. control	117	O	[a] 1 vs. 10		[a] 5 vs. 6		Reduction of costs ERAS group
Ratti [20]	2016	Cohort	EERP open vs. ERP lap. vs. control (HCC)	207	L-O	[a] 12—16 vs. 26		[a] 4 vs. 6	[a] 3 vs. 5	
Kaibori [21]	2017	cohort	ERPvs. control (HCC)	71	O	19 vs. 21		[a] 13 vs. 16		
Wong-Lun-Hing [22]	2017	RCT	ERP open vs. Lap (LLS)	24	L-O	8 lap vs. 36 open	0 lap vs. 9 open	[a] 4 lap vs. 4.5 open	3 vs. 3	
Fretland [23]	2018	RCT	ERP open vs. Lap (CRLM)	280	L-O	[a] 19 lap vs. 31 open	0 lap vs. 0.7 open	[a] 3.6 lap vs. 4.2 open		Same costs for the groups
Ovaere [24]	2018	Cohort	ERP vs. control	229	L-O	[a] 11 vs. 32	0 vs. 0	[a] 4 vs. 6.5		[a] 1912.2€ RAC vs. 3666.7€ control
Tufo [25]	2018	Cohort	ERP 70y vs. 80y	127	L-O	[a] 20 vs. 25.5	1.5 vs. 2.8	6 vs. 6		

Pt: patients; RCT: randomized controlled trial; vs.: versus; Lap: laparoscopy; LLS: left lateral sectionectomy/left lobectomy; y: years; ALOS: average length of stay; CRLM: colorectal liver metastasis; HCC: hepatocellular carcinoma.
[a] Statistically significant difference.

Table 3 Meta-analyses.

Author	Year	Comparison	Pt	ERP (D)	Functional recovery (D)	Morbidity (%)	Mortality (%)	Cost effectiveness
Lei [26]	2014	ERP vs. control	372	WMD = −2.32, 95% CI−3.54−1.11; $P < 0.001$		RR = 0.66, 95% CI 0.47−0.93; $P = 0.02$		
Hughes [27]	2014	ERP vs. control	838	2.5−7 vs. 3−11	3−5 vs. 5−6.7	25 vs. 31	5 vs. 7.5	
Ni [28]	2015	ERP vs. control	723	WMD = −2.77, 95% CI−3.87−1.66; $P < 0.00001$		RR = 0.66, 95%CI 0.49−0.88; $P = 0.005$		
Wu [29]	2015	ERP vs. control	1400	WMD = −2.25, 95% CI −3.10 −1.40; $P < 0.00001$		RR = 0.65, 95% CI 0.52−0.81; $P = 0.0001$	RR = 0.98, 95% CI 0.06−15.17; $P = 0.987$	WMD = −0.45, 95% CI −0.78 −0.12; $P = 0.007$
Yang [30]	2016	ERP vs. control	580	MD = −3.31, 95%CI: −3.95−2.67; $P < 0.00001$		OR = 0.34, 95% CI 0.15−0.75; $P = 0.008$		WMD = 1.0, 95% CI 1.49−0.51; $P < 0.0001$
Song [31]	2016	ERP vs. control	634	WMD = −2.71, 95% CI−3.43−1.99; $P < 0.00001$	WMD = −2.30, 95% CI−3.77−0.83; $P = 0.002$	RR = 0.67, 95 % CI 0.48−0.92; $P = 0.01$	RR = 0.98, 95% CI 0.06−15.17; $P = 0.99$	
Ahmed [32]	2016	ERP vs. control	810	MD = −2.74, 95% CI−3.60−1.87; $P < 0.00001$	MD = −2.09, 95% CI− 3.32−0.86; $P = 0.0008$	OR = 0.90, 95% CI 0.66−1.21; $P = 0.48$	OR = 0.68, 95%CI 0.14−3.34; $P = 0.64$	
Li M [33]	2016	ERP vs. control	1027	WMD = −2.24, 95% CI−3.69−0.79; $P < 0.005$		RR = 0.94, 95% CI 0.79−1.12; $P = 0.49$	RR = 0.63, 95% CI 0.19−2.15; $P = 0.46$	
Li L [34]	2017	ERP vs. control	524	WMD =2.72, 95% CI 3.86−1.57; $P < 0.00001$	WMD = 2.67, 95% CI 3.68−1.66; $P < 0.00001$	OR = 0.45, 95% CI 0.30−0.67; $P < 0.0001$		
Zhao [35]	2017	ERP vs. control	996	MD = −3.17, 95% CI−3.99−2.35, $P < 0.001$		OR = 0.52, 95% CI 0.37−0.72; $P < 0.0001$		
Wang [36]	2017	ERP vs. control	2572	WMD = −2.07, 95% CI −2.76 −1.38; $P < 0.00001$		OR = 0.65, 95% CI 0.50−0.84; $P = 0.001$	OR = 0.81, 95% CI 0.31−2.12; $P = 0.67$	SMD = −0.31, 95% CI −0.47 −0.14; $P = 0.0002$

Pt: patients; ALOS: average length of stay; OR: odds ratio; RR: relative risk; MD: mean difference; WMD: weighted mean difference; CI: confidence interval; SMD: standardized mean difference.

loss > 10—15%, severe malnutrition BMI < 18.5 Kg/m^2, Albuminemia < 30 g/L) should be eligible for nutritional correction during the 7 days preceding surgery (which can be put-off for 15 days) [43];
  - proof of the efficacy of preoperative immunonutrition is presently weak. That said, a randomized controlled multicenter study on this topic — PROPILS [44] — was completed in June 2018, inclusions of 400 patients had been planned; the results are awaited with pronounced anticipation;
- perioperative:
  - preoperative steroids (30 mg/kg, 30 min — 2 h before surgery). Administration of methylprednisolone can be carried out prior to hepatectomy on a healthy liver so as to reduce intraoperative stress, without increasing the risk of complications [45]. This measure is nevertheless to be avoided in diabetics;
  - paparotomy: The choice of incision is left to the discretion of the surgeon. That said, it is preferable to avoid ''mercedes'' incision, which is associated with a higher rate of postoperative eventration than ''J'' (Makuuchi) incision and inverted ''L''-shaped incision [46];
  - paparoscopy: The second international consensus conference on laparoscopic liver surgery [47] concluded that for minor resections, laparoscopic approach is now standardized, and that it is associated with less blood loss, shorter hospital stay and fewer complications. Major resections by laparoscopy are not yet considered as standard, and remain limited to expert centers;
  - postoperative drainage. Absence of prophylactic drainage after hepatectomy is not associated with increased risk of complications [48]. However, given the low level of evidence, no learned society has put forward recommendations for or against drainage;
  - prevention of gastric emptying disorders. In cases of hepatectomy or left lobectomy, gastric emptying disorders, which result from contact of the sectioned edge with the stomach, could be minimized by interposing a greater omentum flap;
- postoperative:
  - epidural analgesia is not more advantageous, in terms of attenuated inflammatory response or lessened pain, than multimodal anesthesia including, among other anesthetics, analgesia by cicatricial catheter [49];
  - perioperative and postoperative blood glucose surveillance. Due to the transitory resistance to insulin induced by surgical stress, hyperglycemia is frequently noted. As a result, insulin treatment must be initiated at an early phase of the hepatectomy so as to maintain normoglycemia (80—120 mg/dL). Preoperative oral carbohydrate supplementation seems to reduce resistance to insulin following hepatectomy [4].

Use of generic elements as a ''hard core'' to be supplemented and enriched by specific elements allows for elaboration of a fully complete ERP likely to dynamically evolve as scientific knowledge advances.

The results of ERP in liver surgery

Improved postoperative recovery is, by definition, central to ERP. In order for its efficacy to be assessed, recovery must be measured as objectively as possible by means of one or more indicators. In this review we shall focus on different indicators or primary endpoints such as morbidity, mortality, average length of hospital stay (ALOS) and the economic repercussions of ERS programs.

Morbidity

Sound data confirm that complications following liver surgery have a negative impact on short-term and long-term survival [39,41].

The objective of the ERP is to decrease complications by reducing response to surgical stress [1—3].

In the different published studies on liver surgery (Table 2), given the low patient population, decrease in complications is not necessarily always significant [7—25].

However, when focusing on the nine most recent studies (2016—2018), including two randomized trials, we have observed a significant decrease in complications in the ERP group (1%—49%) versus control group (10%—64%) [17—25] (Table 2).

A meta-analysis dealing with the impact of ERP following non-colorectal (bariatric, hepatic, pancreatic, esophagogastric, urogynecological) surgery in 6511 patients (3456 ERAS vs. 3055 control) highlighted a 30% decrease in complications in the ERAS group (OR 0.70, 95% CI: 0.56—0.86, $P = 0.001$) [50].

These results are in agreement with those of 11 more selective meta-analyses (26—36) on the impact of ERP in liver surgery in a number of patients ranging from 372 to 2575; once again, a significant decrease in complications in the ERAS group (0.34 < OR < 0.94) (Table 3) appear.

However, when these different results are observed in detail, they are not homogeneous. While all of the meta-analyses under consideration [26—36] are in agreement as to a reduction in grade I complications (according to the Clavien—Dindo definition) in the ERP group, only two of them report a reduction in more severe (Clavien—Dindo grades II—IV or II—V) complications [30,34]. Moreover, the results of these two meta-analyses should be considered with caution given (a) variable definitions of severe complications and (b) the almost exclusively Asian authorship of the studies included, a possible source of bias.

The hypotheses possibly explaining this heterogeneity are based on (a) varied selection criteria (illness severity, resection indications, surgical approach, extension of resection); (b) varied compliance (within a center or between centers) with items in the ERP and; (c) varied appraisals of morbidity.

To conclude, an overall decrease in complication rates in the ERPs is accompanied by similar readmission rates [31,36], even when analyzing the sub-groups in randomized (OR = 2.10, 95% CI = 0.31—14.24, $P = 0.45$) and non-randomized (OR = 0.95, 95% CI = 0.66—1.36, $P = 0.79$) studies [36].

Mortality

There were no significant differences between the ERP group and the control group in either the studies [7—11,13—18,22—25] or the meta-analyses [27,29,31—33,36] (Tables 2 and 3). One of the explanatory hypotheses is that mortality subsequent to a hepatectomy remains a relatively rare event. What is more, in none of the studies was mortality considered as the primary endpoint; lastly, the size of a sample allowing a major difference in mortality to be underscored would be much greater than that of all the studies published up until now.

Length of hospital stay

Length of hospital stay has long since been considered as an indirect marker of recovery and of health care system performance [51].

Generally speaking, ERP in hepatobiliary surgery is associated with pronouncedly shortened hospital stay. A recent European case-control study compared ERAS versus standard care pathways in hepatobiliary surgery in 100 patients ($n = 50$ ERP, $n = 50$ control) who were matched with regard to extent of resection, tumor location and open/laparoscopic surgical approach. In the ERP group, a reduction of 38% (2.5 days) in length of hospital stay (4 days ERAS group vs. 6.5 days control group, $P < 0.001$) was observed, but there was no significant difference in terms of postoperative complication or hospital readmission rate [24].

The meta-analyses in liver surgery taking this type of indicator into consideration reported a mean reduction in length of hospital stay of 2.07 to 3.31 days in the ERP group [26–36] (Table 3).

Using these data, we may summarize by concluding that application of an ERP program in liver surgery brings about a mean reduction in length of hospital stay (duration) of 2.3 days (Table 2). However, non-medical logistics-related factors can also determine length of hospital stay and, in some cases, delay a patient's return home. Some of the most common factors are: absence of a family network or home help services, incompatibility between the theoretical date of discharge and its organizational feasibility (no discharge over the weekend, no medical products available at the town pharmacy, etc.) [42]. Moreover, in some cases a patient may fulfill the existing discharge criteria but experience ''cultural'' anxiety regarding a return home considered as premature [42,51]. The time interval between a patient's surgical intervention and that person's functional recovery seems to be a more objective parameter than length of hospital stay, especially insofar as logistical constraints may vary between one center or country and the next. From a medical standpoint, authorization for discharge (on medical indication) is justified when the listed consensual criteria for functional recovery [52,53] have been fulfilled.

Functional recovery

Two studies that have considered functional recovery time as an evaluation criterion report different results. A first cohort study of 184 patients comparing the periods before and after initiation of an ERP failed to show differences in either functional recovery time (5 vs. 5 days, NS), or length of hospital stay (6 vs. 6 days, NS) [13]. By contrast, a second randomized controlled study of 91 patients comparing an ERP to a control group with a standard program showed a 50% reduction in functional recovery time (3 vs. 6 days, $P < 0.001$) [11].

While the first study [13] did not specify the list of criteria for authorized discharge, the second study [11] applied the following criteria:

- good tolerance of oral nutrition;
- good pain control by oral analgesics;
- independent mobilization;
- normal or improving bilirubin levels;
- the patient's wish for discharge from hospital.

The two meta-analyses employing this indicator reported a relative difference in mean functional recovery time of −2.30 days, (95% CI −3.77 −0.83; $P = 0.002$) [31] and − 2.67 days (95% CI −3.68–1.66; $P < 0.00001$) [34] in favor of the ERP group.

''Supplementary'' hospitalization time is defined as the difference between functional recovery time and actual length of hospital stay. In the Orange II trial (left lobectomy: laparoscopic vs. open surgery), it averaged 20 to 40%, and was attributed to logistical reasons in 38 to 46% of cases, and to medical reasons in 8 to 15% [22].

Economic impact

ERP often bring about health care savings in digestive surgery [53], which may be explained by less time spent in ICUs, reduced consumption during medical treatments (drainages, intravenous therapies, etc.) and a lessened need for biological and imagery-based examinations [17], which may be associated with a lower rate of complications and/or standardized care pathways [17].

In hepatobiliary surgery, on the other hand, up until now ERP has shown no significant impact on the aforementioned medico-economic aspects.

A study carried out in the United States focusing on reduction of unnecessary expenses and wasted resources demonstrated that ERP implementation in liver surgery was associated with a 41% decrease of the additional costs inherent to laboratory examinations and a 22% diminution of expenses related to medical treatment [19].

However, two recent European studies failed to observe any overall economic effect [17,24]. Detailed analysis paradoxically showed an increase in costs incurred during the intraoperative period, the augmentation being due to a heightened percentage of operations performed by laparoscopy [17,24] and to use of an ultrasound dissector (Cavitron Ultra Sound Aspirator: CUSA) [24] in the ERP group. Cost reduction during the postoperative period in the ERAS group may be attributed to shortened hospital stays and lessened complications; so it is that the balance sheet was at the ''break-even point'', notwithstanding the expenses necessarily entailed by ERP implementation.

One must not forget that whether in the operating theater or in intensive care, length of hospital stay is strongly contingent on the habits prevailing in different centers and countries. That is why the most relevant indicator is not absolute difference, but rather relative difference before vs. after implementation [17].

Even though three meta-analyses pertaining to 580, 1400 and 2572 patients respectively reported a significant reduction of hospitalization costs [29,30,36] in the ERP group, interpretation of these findings should take into account the geographical heterogeneity of the studies (Asia, Europe, the United States) and the inclusion of patients operated laparoscopically, a confounding factor for cost increase.

To sum up, only a small number of the randomized controlled studies on ERPs have dealt with the relevant economic data, and they are marked by pronounced methodological biases [53].

The role of laparoscopy in ERPs

Taken alone, when compared with open surgery, mini-invasive surgery is associated with more rapid recovery, which is largely explained by reduced inflammatory response [54].

In digestive surgery, several studies have focused on the role of laparoscopy in an ERP. In a review of the literature, it was found that laparoscopically operated patient groups in an ERAS program had less lengthy hospital stays and lower rates of readmission at 30 days [42].

In hepatobiliary surgery, a study of the Orange II trial [22] comparing mini-invasive vs. open surgical approaches in left lobectomy and postulating functional recovery as the primary endpoint in an ERP was discontinued due to insufficient inclusion; on the one hand, the investigators noted that ''keyhole'' surgery was preferred in 74% of cases; on the other hand, before the end of the study the surgical community was convinced of the advantages of laparoscopy and did not wish to keep on randomizing the two types of approach.

A second randomized controlled trial involving 280 patients (the OSLO-COMET Trial) and comparing laparoscopic to open surgery in management of liver metastases in an ERP highlighted a 12% reduction in postoperative complications (95% CI: 1.67—21.8, $P = 0.021$) in the mini-invasive group [23]. It should be noted that in this superiority trial, comparison pertained not to the ERP, which was applied in the two arms of the trial, but rather to the chosen surgical approach (laparoscopy versus laparotomy).

A meta-analysis comparing ERP versus standard management in hepatobiliary surgery showed a reduction in length of hospital stay in the sub-group of ERAS patients having undergone laparoscopy (WMD = −3.64, 95% CI = −4.63 to −2.64, $P < 0.00001$) as compared to an ERP sub-group having undergone laparotomy (WMD = −1.79, 95% CI = −2.52 to −1.06, $P < 0.00001$) [36].

Independently of the specific weight of the ERP or of care pathway standardization, the observed benefits finally remain the same: better outcomes and improved recovery. That is why it matters to incorporate laparoscopy into ERAS to the greatest possible extent [17].

Prehabilitation

Prehabilitation represents a proactive process of preoperative optimization, which begins with disease diagnosis and continues up until an operation, the objective being to ameliorate functional reserves in the perspective of surgery [55,56].

Known Prehabilitation measures include physical activity, nutritional support and/or immunonutrition, correction of anemia and psychological optimization. And as is the case with ERP, when each of these interventions was tested alone (unimodal treatment), results were mixed.

Up until now, only one single blind randomized controlled trial in liver surgery testing the effect of 4 weeks of physical activity versus control on 35 patients ($n = 16$ control group, $n = 19$ experimental group) has reported improved cardiopulmonary resistance to effort in the Prehabilitation arm. However, no difference was shown between the two groups in rate of postoperative complications or length of hospital stay [57].

To conclude, up until now no study has been published on multimodal Prehabilitation in liver surgery. Moreover, the level of evidence derived from the studies in digestive surgery favorable to Prehabilitation remains at an early stage; sounder results are awaited before Prehabilitation measures are incorporated into ERPs.

Obstacles to implementation of an ERP

Notwithstanding the high level of evidence of the ERPs, success of initiation, rate of compliance and speed of implementation can vary considerably from one center to the next. Some elements are simpler to put into practice than others, particularly when they are not far from daily routine; examples include prophylactic antibiotic treatment, thromboprophylaxis ... and laparoscopic approach. Other elements are more difficult to put into practice, even when coaching has been carried out; examples include absence of intraoperative drainage, early removal of urinary catheter, absence of opioids and ''policy'' of restrictive intraoperative vascular filling [42].

Frequently cited obstacles to ERP implementation include lack of nursing staff or financial resources, difficulties in communication or collaboration between team members, and natural averseness to change. Moreover, elements of the ERAS protocol with a low level of evidence are perceived as the most difficult, and those with a high level of evidence as the least difficult to incorporate [58].

A meta-analysis of 11 studies in colorectal surgery has shown that out of 19 items in the ERP, only a mean number of 14 were actually used, and that they had little real impact on results [59]. In hepatobiliary surgery, there already exists a certain consensus with regard to elements such as a preoperative sweetened drink, absence of gastric catheter or systematic abdominal drainage, reduction of intraoperative infusions, refeeding and early mobilization, and early removal of urinary catheter [36].

The fact that compliance with the ERP has been one of the keys to its success is well-documented; for example, a French study on 1904 patients, 490 of whom had undergone colorectal surgery, showed that length of hospital stay was inversely proportional to the number of satisfactorily applied items of the ERAS program [60].

Given the obstacles to implementation and the difficulty of determining the relative importance of each component of an ERP, it has been suggested that some degree of flexibility allowing for a personalized rather than a rigorously applied protocol could be proposed as a reflection of the wide-ranging variety of patients and procedures for whom and to which an ERAS program could be applied [61]. Factors facilitating its implementation could include special coordination by a team leader, a motivated multidisciplinary team, training courses and teaching sessions dedicated to the advantages of ERP, and regularly planned audits [42,58].

Conclusions

ERP implementation in liver surgery has been shown to be associated with a significant reduction in terms of postoperative complications, functional recovery time and length of hospital stay; on the other hand, it has failed to modify readmission rates. And while the laparoscopic approach can appreciably improve the results of this type of program, the level of evidence in favor of multimodal Prehabilitation in hepatobiliary surgery has remained low.

However, these conclusions should be modulated by the facts that (a) the available meta-analyses are based on a low number of randomized and cohort studies and (b) they are geographically heterogeneous (Europe, United States, China). In other words, in order to obtain a more precise perspective on the efficacy of ERP in liver surgery, it will be necessary to carry out additional clinical studies.

Disclosure of interest

RB and OS declare that they have no competing interest.

KS declares ties of interest with the Sanofi, MSD and B-Braun laboratories.

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Definition and Prospective Assessment of Functional Recovery After Liver Transplantation: A New Objective Consensus-Based Metric for Safe Discharge

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Standardized discharge criteria are critical to reduce premature discharge and avoid unnecessary hospital stays. No such criteria exist for patients undergoing liver transplantation (LT). To achieve a consensus-based checklist of criteria for safe patient discharge after LT, this mixed-method study included the following: a systematic literature review and expert discussion to draft a first checklist of post-LT discharge criteria, defining patient recovery and indications for hospital discharge (functional recovery); an exploratory online electronic Delphi (e-Delphi) study; a single-center pilot study to test checklist feasibility; and a final e-Delphi study with an extended interdisciplinary expert panel to validate the final checklist. The first round provided a 10-point discharge checklist with 5 patient-centered items derived from discharge criteria after liver surgery and 5 graft-centered items derived from expert discussion. The restricted panel (9 experts) e-Delphi provided 100% consensus after the second round, with slight modifications to the criteria. During the pilot study, 19 of 45 (42.2%) patients included fulfilled the complete checklist (100% of 10 items) after median (IQR) 16 (8-21) days (functional recovery) and a length of stay of 20 (9-24) days. The item with the lowest completion rate was minimum serum tacrolimus level in the target on 2 consecutive blood samples (n = 21; 47%), achieved at 13 (9-15) days. The extended panel (66 experts) e-Delphi provided 95%-98% consensus after the third round, with slight modifications of the criteria. This study provided substantial consensus on discharge criteria after LT. We anticipate that these criteria will be useful in clinical practice to guide patient discharge and increase the comparability of results between future studies.

Liver Transplantation 26 1241–1255 2020 AASLD.
Received February 10, 2020; accepted June 6, 2020.

Abbreviations: ACHBT, Association de Chirurgie Hépato-Pancréato-Biliaire et Transplantation; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CCR, colorectal cancer; CI, confidence interval; DCD, donation after circulatory death; e-Delphi, electronic Delphi; ERAS, enhanced recovery after surgery; GGT, gamma-glutamyltransferase; GReF[2], Groupe de Recherche Français en Greffe de Foie; HCC,

SEE EDITORIAL ON PAGE 1219

Liver transplantation (LT) is a lifesaving[(1)] but resource-intensive therapeutic intervention.[(2-4)] Increasing recipient disease severity,[(2)] decreasing graft quality, and more complex surgical procedures[(5,6)] are recent trends that affect length of stay (LoS) after LT.[(3)]

LoS is considered a relevant surrogate metric of hospital care efficiency and LT resource utilization.[3] However, it can be influenced by nonmedical factors[7,8] and can differ widely across countries and health care systems. Consequently, time to functional recovery (TTFR) may be a more reliable outcome metric than LoS.[8,9] Functional recovery has been defined in digestive and liver surgery (LS) through a checklist[9,10] to justify discharge from hospital once all the criteria are met.[11] Nonmedical reasons are responsible for up to 40% of cases of hospital overstay after LS.[12]

The scant literature published to date on this topic[13] suggests that even in LT, functional recovery may be achieved well in advance of the effective date of discharge. Moreover, a defined set of standardized checklist criteria could serve as an objective metric to compare recovery outcomes after LT across departments and countries to reduce heterogeneity. Such a metric is proposed as an essential tool to evaluate the impact of enhanced recovery after surgery (ERAS), which is gaining traction in the field of LT.

hepatocellular carcinoma; ICU, intensive care unit; INR, international normalized ratio; IQR, interquartile range; IV, intravenous; LLS, left lateral sectionectomy; LoS, length of stay; LS, liver surgery; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; NET, neuroendocrine tumor; OR, odds ratio; PT, prothrombin time; RBC, red blood cell; RCT, randomized clinical trial; SD, standard deviation; T0, minimum serum tacrolimus level; TB, total bilirubin; TTFR, time to functional recovery; UTI, urinary tract infection; VAS, visual analogue scale.

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This study is part of a non–grant-funded Ph.D. project (Raffaele BRUSTIA) on enhanced recovery after liver transplantation.

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A list of members of the Groupe de Recherche Français en Greffe de Foie (GReF²) and the Association de Chirurgie Hépato-Pancréato- Biliaire et Transplantation (ACHBT) Collaborative Group is included in the supporting material.

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DOI 10.1002/lt.25841

To address this deficiency, this study aimed to define a pragmatic, consensus-based minimum set of criteria (checklist) for safe discharge after LT and integration into an enhanced recovery pathway. The specific nature of LT dictated a composite checklist including patient and graft recovery criteria.

Patients and Methods

STUDY DESIGN

After review of similar public health research studies,[14-16] we designed a mixed-method study consisting of 4 parts:

1. A systematic literature review and expert discussion to draft a first checklist of discharge criteria after LT.
2. An exploratory online electronic Delphi (e-Delphi) study with a restricted interdisciplinary panel of experts.
3. A small-scale study to test practical feasibility of the checklist.
4. A final e-Delphi study with an extended interdisciplinary panel of experts to validate the final checklist of criteria for functional recovery after LT.

This study was performed between 2017 and 2019, and was approved by the local institutional review committee (Fig. 1).

SYSTEMATIC LITERATURE REVIEW AND EXPERT DISCUSSION

The predefined discharge criteria indicating functional recovery inform objective decision-making regarding sufficient recovery for further management outside the acute hospital setting.[11] These criteria define functional recovery.

The first round aimed to produce a novel list of clinical, biological, or imaging criteria specifically for LT. A checklist compiled from discharge criteria published for functional recovery after colorectal surgery was used as a starting point.[10,17,18]

A systematic review of functional recovery discharge criteria for LS and LT was then performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[19] to enable adaptation of the initial checklist of criteria. The MEDLINE database was searched through PubMed with a search equation using a combination of specific keywords for functional recovery and LS or LT. The results were manually cross-referenced for

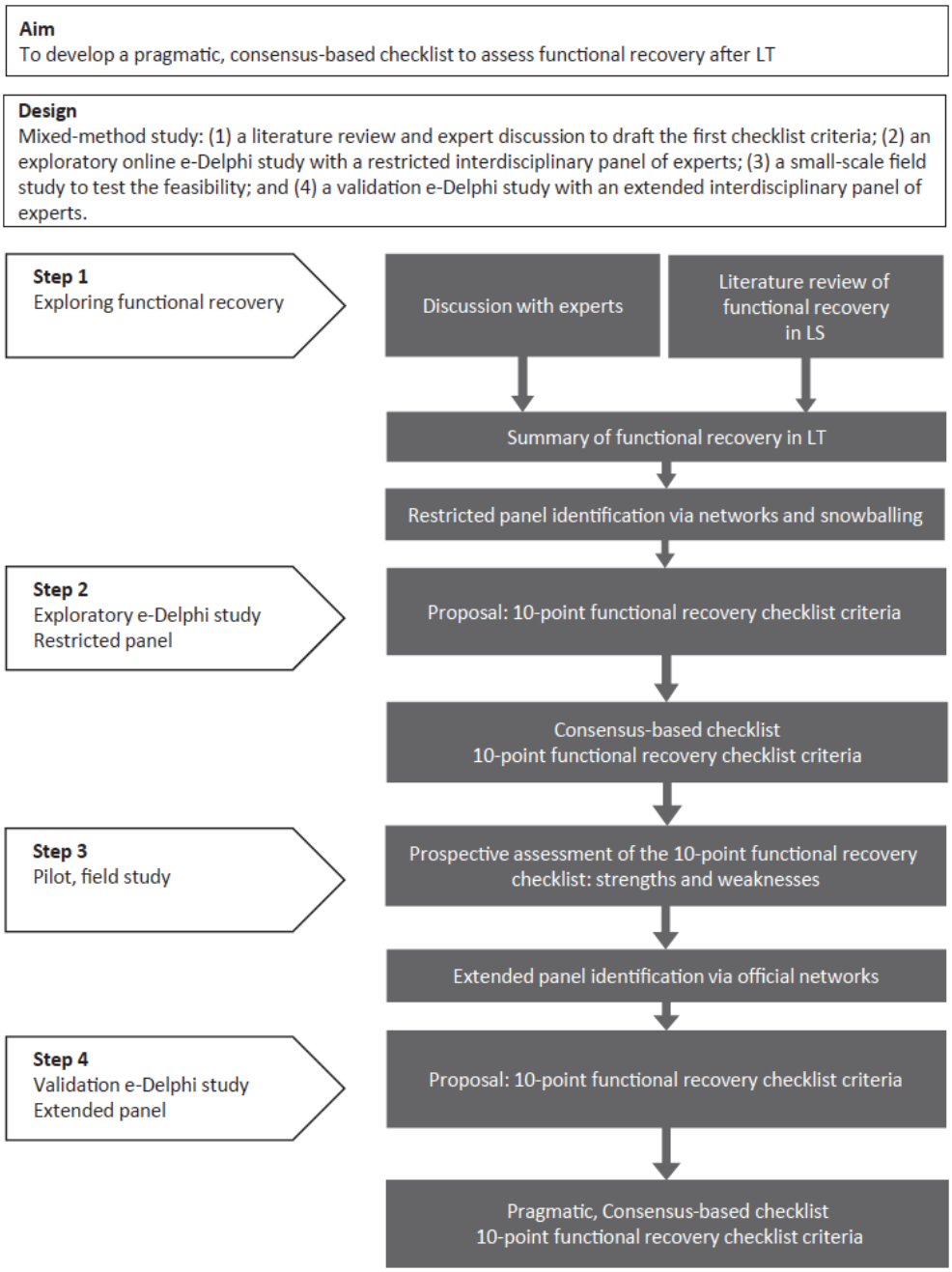

FIG. 1. Flowchart of the study design.

relevant citations. The search was limited to studies published in the last 5 years (2012-2017) to focus on contemporary practice. Studies were considered for inclusion if they focused on adult patients undergoing LT or LS (patients), defined functional recovery or discharge checklists (intervention), regardless of the comparison (comparison), and if they measured TTFR (outcome). We included randomized clinical trials (RCTs) or cohort studies, without restrictions, regarding study location, setting, or period (study design).

One of the authors (R.B.) screened the results of the literature search to select reports for full-text review and inclusion according to the eligibility criteria. For each eligible study, the following data were extracted: year of publication, study design, surgical intervention, checklist of discharge or functional recovery criteria, and study outcome.

Finally, to ensure compatibility specifically for LT patients, 3 experts (2 LT surgeons and 1 LT hepatologist) were consulted to resolve the first checklist, including patient and graft recovery criteria. This version of the checklist formed the basis of the next stage of the project.

SMALL-SCALE e-DELPHI STUDY

The Delphi technique is a structured research tool using questionnaire cycles to build consensus within a panel of experts around a specific topic.[20-22]

The second phase of the study aimed to reach expert consensus on the minimum number of items required to assess and allow safe hospital discharge after LT.

A heterogeneous panel was composed to mirror the multidisciplinary management of LT. Experts in LT surgery, LT hepatology, anesthesiology, and critical care from 3 high-volume French LT centers (Hôpital Pitié Salpêtrière, Paris; Beaujon Hospital, Clichy; Lille University Hospital, Lille) were invited by e-mail in May 2017 to participate. No consensus on the number of participants required for a Delphi panel exists, but a minimum of 10 is considered acceptable.[23] A total of 11 experts were invited for this multidisciplinary panel.

A modified e-Delphi design was used, where a systematic literature review and expert discussion of the first provisional checklist constituted the initial round.[14,24] Online Delphi studies are free of charge compared with paper-based Delphi or face-to-face meetings, and they are particularly suitable when experts are scattered across a country.[24]

We consequently predefined a 3-phase sequence of rounds with iterative feedback.[15] The expert panel was given a schematic roll-up of consensus opinion reached after each round, as well as a 2-week period of reflection followed by an e-mail reminder in case of nonresponse. Each expert was solicited up to 3 times after each round. Given the heterogeneity of the experts' skills and attributes, we specified 80% agreement as the acceptable minimum range, rather than strict consensus.

This second phase generated a consensus-based checklist of criteria for safe hospital discharge after LT. This checklist was then used in the third stage, a pilot study to prospectively assess the feasibility of its practical application.

PROSPECTIVE PILOT STUDY OF THE CHECKLIST

The pilot study was designed as a single-center prospective observational study conducted in the LT department of the Hôpital Pitié Salpêtrière, Paris, from February 2018 to April 2019, in compliance with the Strengthening the Reporting of Observational Studies in Epidemiology Statement.[25] The specific aims were to test the clinical utility, feasibility, and acceptability of applying the checklist.

Only 1 investigator (R.B.) was unblinded. Neither the patient nor the senior medical team in charge of the patient were aware of the date corresponding to functional recovery. The functional recovery date assessment did not influence the final discharge decision, which was only based on clinical criteria and the final judgment of the senior medical team. The investigator (R.B.) did not contribute to the final discharge decision. An incomplete checklist (1 or more items not fulfilled) consequently had no influence on the decision to discharge patients. All adult patients (≥18 years) receiving a whole or split deceased donor graft and undergoing primary LT were eligible for enrollment in this study. All patients were informed of the purpose and procedures of the study and consented to participation.

Patients receiving a combined kidney-liver transplantation, heart-liver transplantation, and retransplantation were excluded. Additionally, LoS longer

than 2 months (60 days) after LT was considered a reflection of major comorbidities and complications; in such cases, the discharge criteria were considered inappropriate, and the patients were excluded.

After transfer from the intensive care unit (ICU) to the clinical ward, 1 of the investigators (R.B.) or a junior staff resident (with no role in the final discharge decision) applied the checklist at the bedside during morning rounds every day until discharge. We recorded the postoperative day when each item was achieved, and we considered the first postoperative day on which all criteria were fulfilled as the day of full recovery. If willing, patients were ready for discharge from the hospital on that day.

Patients were discharged to home or to a care facility, depending on their familial, social, and logistic environment.[7,8] Reasons (social, medical, logistic, or other) for earlier or delayed discharge (ie, before or after complete fulfilment of the checklist, respectively) were captured, and complications up to 90 days after discharge were recorded.

Postoperative pain was quantified with using a visual analogue scale (VAS; pain score), and mobility was quantified by monitoring the patient's daily activity or based on nurses' daily records. Tolerance of oral intake (ability to consume more than half of a given meals without adverse nausea or vomiting) was evaluated using the patient's diet record. Surgical or medical complications were clinically monitored comprehensively during the daily ward rounds (checking for absence of intra-abdominal or surgical-site infection, presence or absence of abdominal drain, absence of headache, or mild hand tremors).

Absence of intravenous (IV) therapy was defined as the removal of the central and occlusion venous catheters or removal of any peripheral venous catheters. Blood chemistry parameters were assessed daily, and trough levels of serum tacrolimus were measured every 48-72 hours. Doppler ultrasound was performed daily from postoperative days 1 to 7 and then once a week until hospital discharge. A ward nurse provided patient education regarding immunosuppressive therapy after discharge from the ICU. At 24 hours before the day identified for discharge from hospital, a dedicated nurse from the LT program conducted a 2-hour face-to-face educational session with each patient.

The primary endpoint was the difference in days between TTFR (from LT to the first day with all checklist criteria fulfilled) and LoS (from LT to actual hospital discharge).

Given the hypothesis of a 20% difference between functional recovery and actual day of discharge[26] and an expected LoS of 26 ± 12 days (mean LoS after LT from 2015 to 2017, unpublished data), the study required enrollment of 45 patients to observe a TTFR 20% shorter than LoS, considering a power of 80% and an alpha error of 5%. Categorical variables were reported as percentages, whereas continuous variables were summarized using median and interquartile range (IQR).

Unadjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using a logistic regression univariate model (binomial) for variables associated with the completed discharge checklist: variables with a P value >0.1 were entered in a multivariate model. The final model expressed the adjusted ORs and 95% CIs.

All analyses were performed using R software version 3.6.2 and upward (The R Foundation for Statistical Computing, Vienna, Austria), with *tableone*, *epiDisplay*, *questionr*, and *ggplot2* packages.

NATIONAL e-DELPHI STUDY WITH AN EXTENDED INTERNATIONAL MULTIDISCIPLINARY EXPERT PANEL TO VALIDATE THE FINAL CHECKLIST FOR FUNCTIONAL RECOVERY AFTER LT

On the basis of the findings of phase 3, another e-Delphi study was completed to establish consensus among the French-speaking community concerning the checklist. The limits observed in the clinical applicability of each item were explained to the panel. The comments and opinions of each expert were analyzed to improve the item's applicability.

The same modified e-Delphi design as in phase 2 was used. A heterogeneous panel of experts in LT surgery, LT hepatology, anesthesiology, and critical care were invited to participate. The minimum criteria set to qualify as an expert was a completed clinical fellowship with at least 2 years of experience in the field. To recruit the largest number of potential participants from the French-speaking LT community, e-mail invitations were sent through 2 national scientific associations, Association de Chirurgie Hépato-Pancréato-Biliaire et Transplantation (ACHBT) and

Groupe de Recherche Français en Greffe de Foie (GReF[2]), in July 2019. Although a minimum of 10 experts is considered acceptable, we aimed to recruit at least 40 participants from more than half of the French LT centers to ensure broad consensus across the national LT community.

A predefined, anonymous, Web-based, 3-phase sequence of questionnaire rounds with iterative feedback was scheduled.[15] Before beginning each round, the questionnaires were pilot-tested on 2 LT surgeons from the Department of Surgery, Hôpital Pitié Salpêtrière, Paris, France. Changes in structure and word clarity were made in response to these LT surgeons' feedback. Consensus was reached if more than 80% of the experts rated the item within the highest region of the scale (7-9 on the 9-point Likert scale).[27]

Once consensus was reached for an item, it was removed from subsequent rounds of questionnaires. Experts were given 2 weeks to respond to each round, followed by 2 reminders after 7 and 14 days. An interval of 2 weeks was used to summarize the data between rounds and develop the next questionnaire.

Results

SYSTEMATIC LITERATURE REVIEW AND EXPERT DISCUSSION

The PubMed search yielded 648 records. After screening, 6 studies[12,26,28-31] enrolling 858 cumulative patients (median, 174; IQR, 109-186) fulfilled the inclusion criteria (Supporting Fig. 1). The characteristics of the included studies are summarized in Table 1. The studies included in the review examined enhanced recovery after LS, but none of the studies examined discharge criteria after LT.

The included studies counted either 4[28,31] or 5[12,26,29,30] discharge criteria. Because the criteria were often described using similar terms, we integrated semantic differences to simplify the data and facilitate analysis. Pain control and solid food were reported by all of the studies (n = 6); mobility restored to an independent or preoperative level was reported in 83% (n = 5); normal or decreasing serum bilirubin level or international normalized ratio was reported in 66.7% (n = 4); absence of IV fluid support was reported in 50% (n = 3); and absence of fever was reported in 33.3% (n = 2).

These discharge criteria after LS presented substantial overlap with the discharge criteria after colorectal surgery: tolerance of oral intake, return of

TABLE 1. Characteristics of the Included Studies

Author	Study	Comparison	Patients, n	Laparoscopy/ Open	LoS (Days)	Functional Recovery (Days)	Pain Control	Solid Food	Mobility	Blood Chemistry	No IV Perfusion	No Fever
Wong-Lun-Hing et al.[12] (2014)	Cohort	ERAS high compliance versus low compliance	165	Laparoscopy/open	7	5	x	x	x	x	x	—
Jones et al.[28] (2013)	RCT	ERAS versus control	91	Laparoscopy	4 versus 7*	3 versus 6*	x	x	x	x	—	—
Dasari et al.[29] (2015)	Cohort	ERAS versus control	184	Laparoscopy/open	6 versus 6	5 versus 5	x	x	x	x	—	x
Liang et al.[31] (2016)	RCT	ERAS versus control (laparoscopy)	187	Laparoscopy	6 versus 10*	5 versus 8*	x	x	—	—	x	x
Ratti et al.[30] (2016)	Cohort	ERAS open versus ERAS laparoscopy versus control (HCC)	207	Laparoscopy/open	4 versus 6*	3 versus 5*	x	x	x	x	x	—
Wong-Lun-Hing et al.[26] (2017)	RCT	ERAS open versus laparoscopy (LLS)	24	Laparoscopy/open	4 versus 4.5*	3 versus 3	x	x	x	x	x	—

*Significant statistical difference.

bowel function, adequate pain control with oral analgesia, ability to mobilize, and no evidence of complications based on clinical examination and laboratory tests.[10,17]

The provisional checklist (Table 2, discharge criteria) to form the basis of the following step was arranged by 3 of the study coordinators (R.B., F.C., and O.S.). We decided to keep all of the previously mentioned criteria that are common to digestive and LS, and we added supplementary graft-centered criteria designed to exclude the most common and serious adverse events that occur early after LT, before the discharge decision, such as primary graft nonfunction with or without vascular thrombosis,[32] primary graft dysfunction,[33] or rejection.[34]

The supplementary graft-centered criteria were as follows: minimum serum tacrolimus level (T0) 5 < ng/mL < 10, good compliance with the immunosuppressive regimen, absence of immunosuppression-induced adverse effect (eg, renal failure, tacrolimus overdose), and normal Doppler ultrasound (arterial resistance index between 0.4 and 0.8).

SMALL-SCALE e-DELPHI STUDY

Of the 11 invited experts, 9 participated in the e-Delphi process. The first-round questionnaire was sent in July 2017, and data collection was completed within 2 months. After the first Delphi questionnaire round, consensus was obtained for items 1-3, 5, 6, and 8 (with 89%) but not for items 4 and 7 (with 78%) and items 9 and 10 (with 67%); some experts requested minor revisions. After the second round, 100% consensus was obtained for all the items (Table 2). This consensus-based checklist of criteria for safe hospital discharge after LT was then used in the third stage of the project, ie, the pilot study to assess the practical feasibility of its prospective application.

PROSPECTIVE PILOT STUDY OF THE CHECKLIST

Between February 2018 and April 2019, 129 LTs were performed at Hôpital Pitié Salpêtrière, of which 101 patients were eligible to test the functional recovery criteria. After exclusion of 56 patients (missing data, untraceable data from paper-based nurse charts, or LoS >60 days), 45 were included and considered for this prospective analysis (Supporting Fig. 2). Median age was 58.4 years (52.7-63.9), median Model for End-Stage Liver Disease (MELD) score was 11.5 (8.0-16.5), and median cold ischemia time was 425 (360-530) minutes. Table 3 describes further baseline patient demographic and clinical characteristics, and Table 4 shows the overall fulfilment of each discharge criteria.

TABLE 2. Results of the Preliminary e-Delphi

Discharge Criteria	Round 1, % Agreement	Round 2, % Agreement
1. Adequate pain control with oral analgesics	89%	100%
2. Independently mobile	89%	100%
3. Tolerance to solid food	89%	100%
4. Absence of uncontrolled surgical complications	78%	100%
5. No IV perfusion	89%	100%
6. Normal/declining TB, ALT, AST, and a PT >80%	89%	100%
7. Residual tacrolimus 5 < ng/mL < 10 on 2 consecutive controls	78%	100%
8. Compliance with therapeutic education	89%	100%
9. No immunosuppressive-induced adverse effect	67%	100%
10. Normal postoperative imaging	67%	100%

The complete checklist (100% of 10 items) was fulfilled in 19 (42.2%) patients after median (IQR) 16.0 (8.0-21.0) days (functional recovery), with an observed LoS of 20.0 (9.0-24.0) days. A total of 25 (55.6%) patients were discharged after achieving 90% of the checklist items (9 out of 10) after 13 (5-19) days with an observed LoS of 15 (7-19) days.

The reported reasons for overstay were nonoptimal immunosuppression trough level (n = 15 of 21; 71%) and logistical issues (absence of postdischarge facilities and patient preference; n = 6 of 21; 29%). The item with the lowest completion rate at the time of discharge was item number 7 (T0 5 < μg/L < 10 on 2 consecutive sample controls), with 47% (n = 21) completion at the time of discharge, achieved after median 13 (9-15) days. The rate of patients prematurely discharged with an incomplete 10-point checklist was as high as 57.8% (n = 26). The model was calculated again after removing item 7 (residual tacrolimus 5 < ng/mL < 10 on 2 consecutive samples). With a modified 9-point checklist (removal of the item 7 [Tacrolimus]), the rate of patients discharged prematurely was reduced to 6.7% (n = 3). The graphic relationship between LoS and functional recovery is shown in Supporting Fig. 3. Hospital stay (OR, 1.1; 95% CI, 0.9-1.2; $P = 0.09$), age (OR, 0.9; 95% CI, 0.8-0.9; $P = 0.02$), and Gap in days (OR, 1.4; 95% CI, 1.1-2.0; $P = 0.01$) were subjected to a

TABLE 3. General Characteristics of the Cohort

Characteristics	Values (n = 45)
Recipient	
Sex, male	33 (73)
Age, years	58.4 (52.7-63.9)
BMI, kg/m^2	24.0 (21.5-28.1)
MELD score	11.5 (8.0-16.5)
Indication	
HCC	29 (64)
Refractory ascites	3 (7)
Liver metastasis (from CCR and NET primary)	3 (7)
Alcoholic cirrhosis	3 (7)
Other	7 (16)
Donor	
DCD	2 (4)
Age, years	57 (54-70)
BMI, kg/m^2	24.3 (22.1-28.1)
Split	7 (16)
Intraoperative	
RBC transfusions, n	0 (0-2)
Cold ischemia time, minutes	425 (360-530)
Operative time, minutes	392 (363-446)
Postoperative	
Postoperative complications, Clavien-Dindo classification	
1	9 (20)
2	10 (22)
3	4 (9)
4	1 (2)
ICU stay, days	5.0 (4.0-8.0)
Primary outcome (10 criteria)	
Patients discharged with the complete 10-point checklist	19 (42.2)
Functional recovery, days	16.0 (8.0-21.0)
Hospital LoS, days	20.0 (9.0-24.0)
Gap, days	3.0 (2.5-5.5)
Gap, %	18.5 (11.1-22.5)
Primary outcome (9 criteria, removal of the item 7 [Tacrolimus])	
Patients discharged with the complete 9-point checklist, %	42 (93.3)
Functional recovery, days	13.0 (9.0-20.0)
Hospital LoS, days	18.0 (14.0-21.0)
Gap, days	3.0 (2.0-6.0)
Gap, %	17 (14-29)
Readmission rate	
30 days	3 (6.7)
90 days	10 (22.2)

NOTE: Data are given as n (%) or median (IQR).

univariate analysis. After adjusting the previous variables, age (OR, 0.8; 95% CI, 0.8-0.9; $P = 0.02$) and Gap in days (OR, 1.5; 95% CI, 1.1-2.1; $P = 0.02$) but not hospital LoS were predictors of the completed discharge checklist (Table 5).

TABLE 4. Discharge Criteria

Criteria	Fulfilled at Discharge (n = 45)	Completion Days
1. Adequate pain control with oral analgesics	45 (100)	6.0 (3.0-9.0)
2. Independently mobile	45 (100)	7.0 (5.0-10.0)
3. Tolerance to solid food	45 (100)	4.0 (3.0-7.0)
4. Absence of uncontrolled surgical complications	45 (100)	9.0 (5.0-15.0)
5. No IV perfusion	45 (100)	9.0 (6.0-15.0)
6. Normal/declining TB, ALT, AST, and a PT >80%	45 (100)	5.0 (4.0-8.0)
7. Residual tacrolimus 5 < ng/mL < 10 on 2 consecutive controls	21 (47)	13.0 (9.0-15.0)
8. Compliance with therapeutic education	45 (100)	11.0 (7.0-15.0)
9. No immunosuppressive-induced adverse effect	43 (96)	9.0 (6.0-12.0)
10. Normal postoperative imaging	44 (98)	10.0 (7.0-17.0)

NOTE: Data are given as n (%) or median (IQR).

NATIONAL e-DELPHI STUDY WITH AN EXTENDED INTERNATIONAL MULTIDISCIPLINARY EXPERT PANEL TO VALIDATE THE FINAL CHECKLIST FOR FUNCTIONAL RECOVERY AFTER LT

Among the 192 experts invited, 66 (34.4%) replied. The first-round questionnaire was sent in July 2019, and data collection was completed within 3 months in October 2019. Participants from 20 different LT centers in France (n = 64), Switzerland (n = 1), and Belgium (n = 1) completed all 3 rounds of the e-Delphi process. Supporting Fig. 4 describes further information on the e-Delphi panel. All experts reported a high level of expertise with an average of 14.4-9.1 years of experience.

After round 1, consensus was reached for 7 criteria. Prompted by the panel's suggestions, changes were made to the wording used to describe the criteria, leading to consensus being reached for all 10 criteria after round 2. After minor changes to 5 criteria, a third and last round was performed that further increased

TABLE 5. Results of Univariate and Multivariate Linear Regression Analyses Predicting LoS

	Univariate Analysis			Adjusted Analysis		
Patients (n = 45)	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Hospital stay	1.1	0.9-1.2	0.09	0.9	0.9-1.1	0.94
Sex, male	0.4	0.1-1.6	0.19			
Age	0.9	0.8-0.9	0.02	0.8	0.8-0.9	0.02
Cold ischemia time	1.0	0.9-1.0	0.53			
Donor (reference, DCD)	1.4	0.1-36.7	0.82			
Graft (reference, split)	2.0	0.4-11.6	0.39			
Functional recovery	1.0	0.9-1.1	0.33			
Gap	1.4	1.1-2.0	0.01	1.5	1.1-2.1	0.02
Complications	2.0	0.6-6.9	0.26			

the consensus rate. The other 5 criteria were kept unchanged and omitted from the third round.

Table 6 shows the trend of consensus rating for each criterion across the last 2 rounds (Fig. 2). Table 7 reports the final readiness-for-discharge criteria in English (and the French version is given in Supporting Table 1). Practical examples of a daily filled checklist are available in Supporting Table 2 and Supporting Fig. 5.

Discussion

This is the first study to establish a definition of functional recovery after LT using an e-Delphi consensus process and assess its practical use in routine clinical practice. The hybrid nature of this checklist, combining patient-centered and graft-centered criteria, is pioneering in the field of LT recovery.

The checklist items are based on adequate pain control by oral analgesia; independent mobility; tolerance of oral intake; absence of major uncontrolled surgical, medical, or infectious complications; no IV treatment; improvement in blood test results; plasma level of the immunosuppressive regimen adapted to the patient's individual target level; therapeutic education provided; improvement or stable control of any medical or immunosuppression-related complications; and no complications requiring urgent intervention present on postoperative imaging.

This study generated a user-friendly checklist defining functional recovery after LT. This simple definition will help to investigate the reasons for delayed discharge and aid the removal of logistical or cultural barriers. The checklist may be considered safe if the patient is discharged on the same day of checklist fulfilment because only 1 patient was readmitted within 30 days (for acute kidney injury treated by IV rehydration). The overall 30-day readmission rate for the study was 6.7% (n = 3 of 45 patients). Another strength of this checklist is that the final version reflects the consensus of a large number of experts from multiple disciplines contributing to the care of LT patients.

Moreover, mirroring research already published in LS,[9,26,28,29] this checklist can be used to assess the impact of an ERAS protocol in LT, regardless of the differences between countries and health systems. The comparison of results between clinical trials

TABLE 6. Results of the Large-Scale e-Delphi Process

	Round 2		Round 3	
Panelists (n = 66)	Agreement	Likert Scale Score	Agreement	Mean Likert Scale Score
1. Pain control	98	8.5 (1.2)	—	—
2. Mobilization	98	8.3 (1.2)	—	—
3. Alimentation	96	8.3 (1.2)	98	8.4 (0.7)
4. No complications	96	8.4 (0.8)	—	—
5. No IV perfusions	93	7.9 (1.8)	97	8.4 (1.1)
6. Blood test	89	7.9 (1.5)	—	—
7. Tacrolimus	86	7.7 (1.6)	98	8.5 (0.7)
8. Education	96	8.2 (1.1)	95	8.3 (1.1)
9. Adverse effect	96	8.1 (1.2)	—	—
10. Imaging	98	8.5 (0.7)	97	8.6 (0.8)

NOTE: Data are given as % or mean (SD).

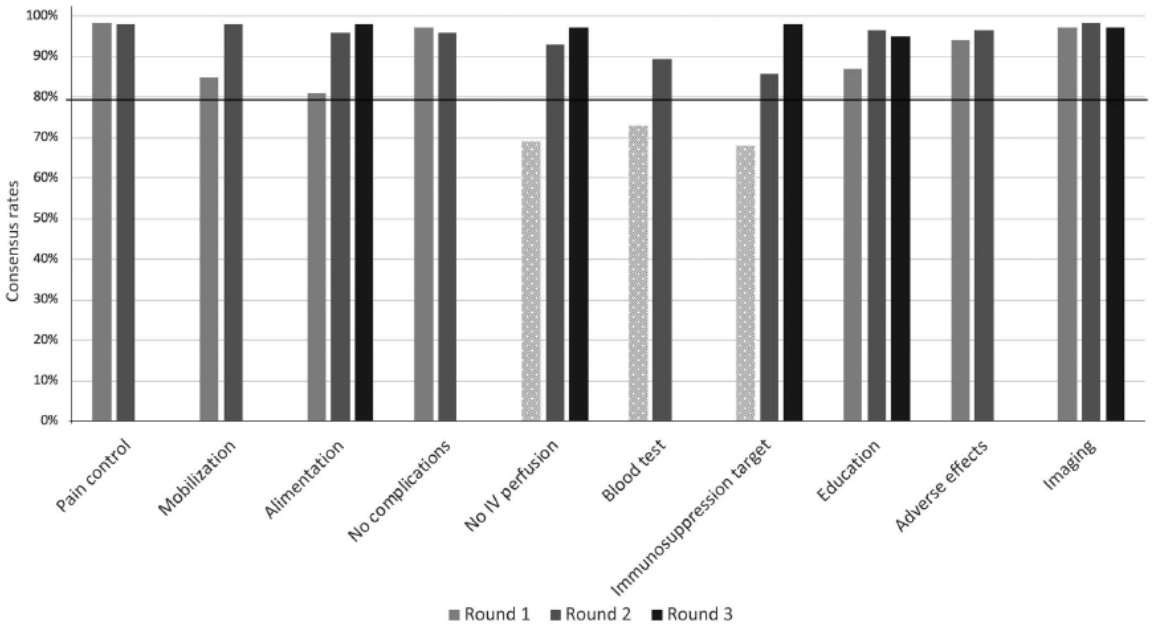

FIG. 2. Consensus rates across the three e-Delphi rounds. The horizontal line represents the bar of consensus, when more than 80% of the experts rated the item within the highest region of the scale (7-9 on the 9-point Likert scale).

that assess metrics of recovery such as LoS are limited by the current lack of any standardized hospital discharge criteria. The use of standardized consensus-based criteria will help to increase the consistency and comparability of outcomes by reducing trial and outcome heterogeneity.

This study detected a gap between functional recovery and LoS, consistent with publications in digestive surgery[8,11] and LS.[26] The median gap of +3 days was mainly related to nonoptimal immunosuppression trough level or logistical issues (absence of postdischarge facilities). The study findings have important implications for patient care and research in LT. The concept of ERAS and safe hospital discharge has reached the sphere of LT, but it remains critical that patients are only discharged once they have reached a degree of recovery sufficient for management as an outpatient. Although similar checklists have been described and validated in other fields of surgery, often within an ERAS program, there is still no clear definition established for functional recovery after LT.

A systematic review of discharge checklists in LS (Table 1), as outlined in the first step of this study, found that the main criteria to determine safe discharge were pain control, intake of solid food, mobility, blood chemistry trending to normality, no IV therapy, and absence of fever. Our LT discharge checklist includes all these items but, in addition, integrates transplant-specific items (individualized immunosuppression trough levels, compliance with therapeutic education, immunosuppression-related adverse effects, and postoperative imaging). On the basis of a proposal by Zeidan et al.,[35] discharge safety may be improved by the assistance of a clinical pharmacist (when available) that uses visual aids for therapeutic education. Additionally, improved discharge planning that allows for effective organization of therapeutic education may increase the rate of discharge, even over weekends.

The main strength of this study lies in its mixed-method design with a step-by-step process encompassing systematic review of the literature, expert discussion, preliminary e-Delphi expert panel, a prospective pilot study, and a larger-scale e-Delphi process involving a multidisciplinary expert panel. Evidence suggests that an online-based process (e-Delphi) can improve the quality of consensus development: it has well-established benefits that

TABLE 7. Criteria to Determine Readiness for Hospital Discharge Following LT: When the Criteria Set Out Here Are Fulfilled, the Patient Is Considered to Have Achieved Short-Term Postoperative Recovery and Should Be Considered Ready for Discharge

Discharge Criteria	Detail
1. Adequate pain control by oral analgesia (VAS <4/10)	• If there was preexisting chronic pain (eg, osteoporotic vertebral fracture), it should be brought back to at least preoperative levels of control
2. Independently mobile (able to walk alone unassisted, able to dress alone or with minimal assistance), and able to get to the Transplantation Department in the event of alarm symptoms (such as fever, pain, or jaundice)	• If hospital recovery is incomplete, patients should have family or caregiver support available at home • Recovery and physical therapy are continued at home (eg, kinesiotherapy or in-home care) or in rehabilitation facilities if recovery is limited or if the patient has preexisting disabilities (eg, fracture, pressure ulcer, or amputation)
3. Tolerance of oral intake	• Patient can cope with oral or enteral nutrition without nausea, reflux, regurgitation, or vomiting limiting intake • IV fluid support should not be necessary to maintain adequate fluid intake and electrolyte balance • If the patient is exclusively on oral feeding, he/she is able to consume at least 1 standard meal per day (including at least 1 main course). The patient should be able to eat alone or with help if he/she has limited autonomy • If required, enteral nutrition (night or daytime) can be organized at home without delay
4. Absence of major uncontrolled surgical or medical/infectious complications.	• Complications requiring local care or antibiotic regimen (eg, Surgical Site Infections, UTI) do not preclude discharge
5. No IV treatment	• When an IV drug regimen is required, it may be switched to per os, Intramuscular, or Subcutaneous or continued as IV treatment at home without delay (by a caregiver).
6. Improvement of blood test results	• Blood chemistry tests tend toward normalization. • Indication of normal or declining cytolysis (AST, ALT) and cholestasis (TB, GGT, ALP). • Synthesis functions (prothrombin ratio, factor V) are stable or increasing
7. Plasma concentration of the immunosuppressive regimen is adapted to the patient's target level	• If blood test results are not yet back to normal, the patient must have access to blood test monitoring (public or private laboratory) and short-interval follow-up consultation (eg, during the first week after discharge)
8. Patient given appropriate therapeutic education (eg, on their immunosuppressive therapy, glycemic control, or insulin therapy, if required)	• A treatment information session (or structured therapeutic education program when available) is provided by a health professional (clinical pharmacist or coordinating nurse) • If the patient is unable to self-manage treatment, information or therapeutic education is provided to their family or caregivers • If treatment is complex to coordinate/manage, discharge to home can be considered with a caregiver provider or home-discharge facility (eg, while waiting for a short admission to the diabetology clinic for therapeutic education on insulin therapy)
9. Improvement or stability of any medical or immunosuppressive-related complication	• Improvement or stability in conditions such as, for example, renal failure, tacrolimus overdose, or pancytopenia
10. No complications requiring urgent intervention on imaging before discharge.	

promote construction of knowledge and reflection and the online feedback-based process is a structured, rigorous, and rapid method that removes logistical challenges, peer pressure, and group-think scenarios.[20,21,24] This approach met our aim to reach multidisciplinary consensus. The online design of the study allowed experts to complete all questionnaires quickly and anonymously, preventing domination by any individual and at zero cost. As an example, the consensus on item 7 (serum tacrolimus level) steadily improved through the multistep approach. Although its clinical applicability in the initial pilot study was poor, the 3 rounds of the larger-scale e-Delphi consensus process progressively allowed substantial changes to this item (especially by removing any numerical cutoffs and allowing discharge for patients with inadequate levels but with strong recommendations on monitoring and follow-up, which might increase adherence).

This study has some limitations. The final checklist for safe discharge reflects the opinion of French and French-speaking experts, and different cultures and organizations may have different approaches to recovery and to recovery recommendations. This may be particularly true in the US system of care, where skilled nursing facilities are used. The checklist might be considered to assess the readiness for discharge from these facilities, rather than from hospitals.

The external validity of the checklist will need to be explored to assess its applicability in other centers, particularly with respect to the sickest patient groups (higher MELD score, older individuals, and patients with comorbidities). In this study, the relatively low MELD score (median, 11.5) is related to the high number of patients transplanted for hepatocellular carcinoma (HCC; n = 29) and liver metastases (n = 3), representing 68.8% of the cohort. A similar process can be used to construct a similar checklist for different target populations, eg, pediatric patients or LT combined with other organs (heart, kidney, lung, or pancreas). No patients were involved in the 2 e-Delphi phases, which may also be considered a limitation of the study.

In conclusion, this work led to a consensus-based checklist of 10 pragmatic criteria to advance safe discharge after LT. These criteria are easy to collect, and checklist completion is achievable in clinical settings. Further studies are needed to validate its applicability in multicenter and international settings.

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Appendix

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8.5 ANNEXE 5

Transplantation Publish Ahead of Print

DOI: 10.1097/TP.0000000000003808

Guidelines for Perioperative Care for Liver Transplantation: Enhanced Recovery After Surgery (ERAS) Society Recommendations

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FINANCIAL SUPPORT This study is part of a nongrant-funded PhD project on enhanced recovery after liver transplantation.

CONFLICT OF INTEREST: None.

AUTHORS CONTRIBUTIONS

RB performed the systematic review, planned the e-delphi consensus, wrote and edited the manuscript;

AM performed the systematic review, participated to the consensus, wrote 1 part of the manuscript and edited the manuscript;

SS performed the systematic review, participated to the consensus, wrote 1 part of the manuscript and edited the manuscript;

ES and DP performed the systematic review, participated to the consensus, revised critically and edited the manuscript;

SW and ND participated to the consensus, offered insights, revised critically and edited the manuscript.

All the remaining Authors participated to the consensus, revised critically and edited the manuscript.

OS moreover supervised the strategy and revised critically and edited the manuscript.

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ABSTRACT

BACKGROUND:

Enhanced Recovery After Surgery (ERAS) is a multimodal, evidence-based, program of care developed to minimize the response to surgical stress, associated with reduced perioperative morbidity and hospital stay. This study presents the specific ERAS Society recommendations for liver transplantation (LT) based on the best available evidence and on expert consensus

METHODS:

PubMed and ClinicalTrials.gov were searched in April 2019 for published and ongoing RCTs on LT in the last 15 years. Studies were selected by 5 independent reviewers, and were eligible if focusing on each validated ERAS items in the area of adult LT. An e-Delphi method was used with an extended interdisciplinary panel of experts to validate the final recommendations.

RESULTS:

Forty-three articles were included in the systematic review. Consensus was reached among experts after the second round. Patients should be screened for malnutrition and treated whenever possible. Prophylactic nasogastric intubation and prophylactic abdominal drainage may be omitted, and early extubation should be considered. Early oral intake, mobilization and multimodal-balanced analgesia are recommended.

CONCLUSIONS:

The current ERAS recommendations were elaborated based on the best available evidence and endorsed by the e-Delphi method. Nevertheless, prospective studies need to confirm the clinical use of the suggested protocol.

PROSPERO CRD4201913279

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BACKGROUND

Enhanced Recovery After Surgery (ERAS) is a multimodal, evidence-based, program of care developed to minimize the response to surgical stress.[1,2]

The concept is based on a multidisciplinary team working around the patient, to ensure the synergic application of 20 program elements throughout each phase of the patient's journey.[2]

The implementation of ERAS recommendations in major surgery domains including colorectal,[3] pancreatic[4] and liver[5] surgery is associated with an improved recovery with a reduction in postoperative complications and hospital length of stay but without an increase in readmission rates .[6–8]

Liver Transplantation (LT) is a life-saving treatment for end-stage liver disease (ESLD),[9] with 1 and 5 years survival of 83%-92% and 71%- 87%, respectively.[10–13] In spite of these positive survival results complications are common and frailty, preoperative comorbidities, surgical challenges and postoperative immunosuppression are responsible of 40%-92% all-confounded morbidity.[10,14–18]

Liver surgery and liver transplantation share many points in common and the same principles of enhanced recovery may apply for liver transplantation. Nevertheless, little evidence exists on the application of an ERAS program in LT, apart from 2 feasibility studies reporting on the effectiveness of such a program on the length of stay after LT.[19,20]

This study aims to develop the specific ERAS Society recommendations for liver transplantation based on the best available evidence and on expert consensus.

METHODS

An international panel of liver transplant surgeons and anaesthesiologists from 12 international centers, including the steering committee (Liège-Belgium, Sao Paulo-Brazil, Montréal-Canada, Torino-Italy, Pisa-Italy, Kyoto-Japan, Groningen-Netherlands, Paris-France, Alicante-Spain, Genève-Switzerland, Portland-US, Edinburgh-UK) were invited to participate.

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These guidelines were realized according to the Recommendations from the ERAS® Society for standards for the development of enhanced recovery after surgery[21] and the Appraisal of Guidelines, Research and Evaluation (AGREE) recommendations,[22] with LT surgeons, anaesthesiologists or LT hepatologists as target users.

Items analysed

The ERAS Guidelines for Liver Surgery[5] were used as working basis to develop the present guidelines, including the list of examined items. Hence, given some particular aspects of LT, a preliminary draft including the list of items on which the guideline would focus on was submitted for approval to all the experts. These agreed to remove the Mechanical/Oral bowel preparation item, considered as irrelevant in LT context, and "prehabilitation", "temporary portocaval shunt", "early extubation", "postoperative education" items were added. The final list included 22 items. According to the methodology used for the development of the previous ERAS guidelines on Liver Surgery[5], 22 different search equations were realized, 1 for each keywords group defining a validated ERAS item (preadmission counselling, prehabilitation, fluid and carbohydrate loading, no prolonged fasting, no/selective bowel preparation, antibiotic prophylaxis, thromboprophylaxis, no premedication, short acting anaesthetic agents, temporary portocaval shunt, mid-thoracic epidural anaesthesia, no drains, avoidance of salt and water overload, maintenance of normothermia, no nasogastric tubes, prevention of nausea and vomiting, early extubation, early removal of catheter, early oral nutrition, early mobilisation, nonopioid oral analgesia, stimulation of gut motility, postoperative education, audit of compliance and outcomes).

Literature search and data extraction

The coordinator centre (Pitié Salpêtrière, Paris, France) realized a digital search Medline through PubMed for published studies and ClinicalTrials.gov for ongoing trials, focusing on each validated ERAS items in the area of liver transplantation. Each single validated ERAS

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item was defined by a group of specific keywords extracted from official ERAS guidelines and 1 pilot study on ERAS and LT.[2,3,5,19,23,24]

Participants/population

Human adult patients (18 years or older) undergoing LT, with a graft (whole or split) coming from a deceased (after brain or cardiac death) or living donor, no matter the indication for LT. Articles focusing on re-transplantation or combined LT (with kidney, hearth, lung, pancreas or intestine) were not considered because of different patterns of morbidity and mortality. Studies focusing on paediatric LT and experimental studies including animals were not considered for inclusion.

Intervention(s), exposure(s)

No restriction on the type of intervention tested were applied, provided that the target population is composed of patients undergoing LT. According to the ERAS protocol, interventions could be during the preoperative, intraoperative or postoperative period immediately after LT.

Comparator(s)/control

None

Main outcome(s)

Outcomes assessed: all primary outcomes reported in the result section were extracted with the related definition, and severity score when provided. Measures of effect were classed (e.g. clinical outcome, surgical outcome, mortality, morbidity, recovery outcome, patients reported outcomes[25]) as well as the direction of effect (in favour vs against).

Setting

No restriction on study location or settings were applied.

Language

We will consider articles reported in English, French, German, Italian or Portuguese. Studies

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in other languages will be included only if the translation can be adequately obtained through Google translate.

Types of study included

Were considered for inclusion prospective or retrospective studies (cohorts or registry), case control or randomized clinical trials (RCT). If relevant, reviews and meta-analyses were evaluated for inclusion. Case reports were excluded, as well as any study including less than 10 patients. Abstracts, letters to the editor or conference posters were not considered for inclusion because of the lack of complete methods and results description.

Manual cross-references among the included studies were searched, for relevant related citations. The searches were done from 15/04/2019 – to 28/04/2019. The results of the literature research were screened by 5 investigators (2 surgeons: RB, DP, 3 anaesthesiologists: AM, SS, ES) on the basis of title and abstract through an on-line support.[26] Doubtful inclusions were resolved through discussion. A standardized data collection form, specifically designed for the purpose of this study, was used by 3 investigators for data extraction from published articles or for ongoing trials at ClinicalTrials.gov. After selection and inclusion for qualitative analysis, each trial was scored for quality (Risk of Bias tool - Cochrane collaboration's tool,[27] Jadad score,[28] and GRADE[29]).

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement[30]: the protocol was registered on the International Prospective Register of Systematic Reviews[31] current May 2019 (PROSPERO CRD42019132798).

Recommendation drafting

Based on the results of the literature search, a working group composed by 3 investigators (RB, AM, SS) prepared, for each item

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- *The supporting text*: concise, focused on relevant publications to support the evidence of the recommendations. If necessary, a few additional publications could be cited to support and explain the supporting text but without providing an extensive review of the literature.
- *The recommendation*: was defined as a statement that contained a course of action such as a preventive or treatment activity. Recommendations should contain the verbs can/may (weak), should or shall (strong) depending on the recommendation grade. Recommendations were based not only on quality of evidence but also on the balance between desirable and undesirable effects and on the values and the preferences. The latter implies that, in some cases, strong recommendations may be reached from low-quality data and vice versa.[29]
- *The grade of evidence* based on the Oxford level of evidence[32] (ranging from 1 to 5) and GRADE quality of evidence[29] (''high'', ''moderate'', ''low'' and ''very low''). Shortly, the GRADE assessment approach provides a structured way to consider key factors that may increase or decrease confidence towards a synthesized body of evidence, and particularly on the quality of evidence in the body of literature supporting the evidence itself. The final analysis may be classified as high, moderate, low and very low depending on the importance of outcomes, risk of bias, heterogeneity, indirectness, imprecision and publication bias.[21]
- *The strength of recommendation* There was not necessarily a 1:1 relation between strength of the recommendation (strong/weak) and the quality of the evidence. The strength of recommendation should also take into account criteria such as consistency of study results, clinical relevance of endpoints (outcomes) and effect sizes, risk-benefit ratio, patient preferences, application to the relevant patient group, application to

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healthcare setting, legal and economic considerations. Based on these criteria, upgrading or downgrading of grades of recommendation was allowed.[33]

Consensus process (Delphi)

The strength of recommendation, quality of evidence and conclusions were assessed and agreed by a 3 round e-Delphi process. The Delphi technique is a structured research tool for building consensus within a panel of experts around a specific topic through multiple interactions with questionnaires.[34–36] We sought to compose a heterogeneous panel in order to bring a range of disciplinary viewpoints, mirroring the multidisciplinary management of LT across caregivers and the "core philosophy" of multimodal ERAS management. Experts in LT surgery, anesthesiology and critical care from 12 high-volume LT centers (Liège-Belgium, Sao Paulo-Brazil, Montréal-Canada, Torino-Italy, Pisa-Italy, Kyoto-Japan, Groningen-Netherlands, Paris-France, Alicante-Spain, Genève-Switzerland, Portland-US, Edinburgh-UK) were contacted by e-mail in November 2019 and invited to participate. There is no consensus on the sample size of participants required for a Delphi panel, but a minimum of 10 is considered acceptable.[37] Here we invited 27 experts in this phase.

We used the modified electronic Delphi design, where the 'modified' term refers to the use of systematic literature review and expert discussion to drive the first provisional checklist for the initial questionnaire round rather than open interview on a broad list of items.[38,39] Online Delphi studies are free of charge compared to paper-based Delphi or face-to-face meetings, and are particularly suitable when experts are scattered across countries.[38] We consequently predefined a 3-phase sequence of rounds with iterative feedback.[40] We solicited each expert up to 3 times after each round. Consensus was considered as reached if more than 80% the of experts rated the item within the highest region of the scale (7, 8 or 9 on the 9-point Likert scale).[41] Once consensus was reached for a given item, that item was removed and no longer proposed in the following round. Experts were given 2 weeks to respond to each round,

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followed by 2 reminders to complete the questionnaire that were sent out after 7 and 14 days. A 2-week interval between rounds was used to summarize the data and develop the next questionnaire.

We did not plan an external revision of final recommendations, but an updating procedure will be proposed every 5 years.

RESULTS

Among the 2685 references identified by the PubMed search, 43 were included. From the search on Clinicatrials.gov, we identified 62 references and included 6 ongoing trials. The selection process is detailed in Figure 1, and the complete list of trials can be found in Supplementary_material_study_list http://links.lww.com/TP/C225 .

Characteristics of the included trials

Among the included studies, 40 (93%) were from single centers, including a median of 105 (38.5-171.5) patients. The design was prospective in 25 (55.8%) of included studies, with 12 (27.9%) randomized. The experimental intervention was nonpharmacological, pharmacological and combined in 23 (53.5%), 19 (44.2%) and 1 (2.3%) of studies.

The indication of LT was detailed in 32 studies (74.4%), with the use of deceased donor graft, LDLT or both reported in 15 (34.9%), 9 (20.9%) and 3 (7.0%) of cases, respectively. The reported level of evidence according to the GRADE[29] was rated as high in 3 (7%), moderate in 16 (37.2%), low in 16 (37.2%) and very low in 7 (16.3%) of the 43 published references. More details in Table 1.

e-Delphi process results.

Among the 27 experts invited, 21 (81%) replied from 12 international LT centers reporting a median volume of 70 (40-112.5) LT per year: n=7 centres reported low-intermediate volume (<75 LT/year[42–44]), and 5 high-volume (>75-100 LT/year[42–44]).

The round-1 questionnaire was sent in November 2019, and data collection was completed

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within 3 months, in February 2020. Figure 2 gives further information on the e-Delphi panel, with an average 15.7±7.86 years of experience. After round 1, consensus was reached for 16/22 criteria, with 2 of them requiring minor rewording. Changes were made to the wording used to describe the criteria, prompted by the panel's suggestions, and after round 2, consensus was reached for all the remaining criteria. The figure 3 shows the trend of consensus rating for each criterion across the last 2 rounds.

Within the Table 2 are summarized the ERAS recommendations for each item and the respective level of evidence, and in the supplementary_material_supporting_text http://links.lww.com/TP/C225 is exposed the rationale for each recommendation.

CONCLUSIONS

This systematic review highlights how current available evidence on enhanced recovery pathways in liver transplantation is scarce, and lacks standardization. The highest level of evidence (level 1 or 2) was available for 13 out of 22 items. While the value of ERAS pathways has now been demonstrated in liver, colorectal and pancreas surgery showing benefit in morbidity, cost and medico-economic outcomes, there is a clear need to perform high-quality studies to confirm the benefit of ERAS pathways in liver transplantation. In conclusion, the proposed ERAS pathway for liver transplantation is based on the best available evidence, which still needs to be further explored.

To allow benchmarking and comparison across trials using the new proposed liver transplantation ERAS recommendations, there is a need for consensual and standardized outcomes in liver transplantation, which are currently lacking.[25] In this line, a standardized and consensual checklist criteria to assess readiness for hospital discharge (or functional recovery) after LT was recently proposed.[45] Moreover, as highlighted by Muller X. et al[46] in a multicentre analysis to define benchmarks in LT, 82% of patients developed at least 1

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complication during 1-year follow-up. When the latter is taken into account, probably the weight of morbidity as an outcome in ERAS guidelines validation should be reconsidered. Lastly, as with all existing ERAS pathways, the assessment of adherence to the protocol (compliance) is of utmost importance, and the compliance with the new proposed liver transplantation ERAS protocol should be documented, as part of further trial to allow benchmarking.

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TABLE 1 Characteristics of the selected studies.

TABLE 2 Summary of ERAS recommendations for each item and the respective level of evidence.

FIGURE 1 Flowchart of included studies

FIGURE 2 Characteristics of the expert panelists (experience, specialty, and LT volume).

FIGURE 3 Trend of consensus rating for each criterion across the e-Delphi rounds. The asterisks on the items 4 (antibiotic prophylaxis) and 13 (fluid and blood management) mean that an agreement was reached within the first round, but major rephrasing was proposed by the panel. The consensus rate was maintained above 80% for these 2 items during the second round.

Supplementary_material_study_list http://links.lww.com/TP/C225 . List and characteristics of included studies

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Table 1. Characteristics of the selected studies

	Overall (n=43)
Publication Year	
2000	1 (2.3%)
2002	1 (2.3%)
2007	1 (2.3%)
2009	1 (2.3%)
2010	3 (7.0%)
2011	2 (4.7%)
2013	2 (4.7%)
2014	5 (11.6%)
2015	4 (9.3%)
2016	7 (16.3%)
2017	8 (18.6%)
2018	4 (9.3%)
2019	4 (9.3%)
Location Corresponding Author	
Africa	1 (2.3%)
Asia	8 (18.6%)
Australia	2 (4.7%)
Europe	16 (37.2%)
North America	13 (30.2%)
South America	3 (7.0%)
Study Design	
Cohort	17 (39.5%)
RCT	12 (27.9%)
Case-control	7 (16.3%)
Before-after	6 (14.0%)
Outcome research	1 (2.3%)
If observational	
Prospective	24 (55.8%)
Retrospective	19 (44.2%)
If RCT	
Unblinded	8 (18.6%)
Double blind	4 (9.3%)
Single blind	1 (2.3%)
Single/multicenter	
Single center	40 (93.0%)
Multicenter, National	2 (4.7%)
Multicenter, International	1 (2.3%)
Total number of patients enrolled	
Mean (SD)	227 (496)
Median [25th, 75th]	105 [40, 171]
Level of Evidence, Oxford	
1	12 (27.9%)

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2	15 (34.9%)
3	7 (16.3%)
4	9 (20.9%)
Indication of LT (reported)	
Yes	32 (74.4%)
No	11 (25.6%)
Type of graft	
Deceased donor	15 (34.9%)
LDLT	9 (20.9%)
Both	3 (7.0%)
Not detailed	16 (37.2%)
Timing of intervention	
Preoperative (including prehabilitation)	3 (7.0%)
Intraoperative or perioperative	24 (55.8%)
Early postoperative (up to discharge)	11 (25.6%)
Late postoperative or followup	5 (11.6%)
Class of intervention	
Medical treatment (including antibiotherapy)	13 (30.2%)
Anesthesiology	11 (25.6%)
Nutritional support	6 (14.0%)
Physical therapy	5 (11.6%)
Other	4 (9.3%)
Surgical technique	3 (7.0%)
Psychology education	1 (2.3%)
Type of intervention	
Non pharmacologic	23 (53.5%)
Pharmacologic	19 (44.2%)
Combined	1 (2.3%)
Impact on Morbidity	
Decreased	11 (25.6%)
No difference	13 (30.2%)
Unclear	2 (4.7%)
Increased	1 (2.3%)
Impact on Mortality	
No difference	16 (37.2%)
Decreased	1 (2.3%)
Unclear	1 (2.3%)
Impact on Liver Graft Dysfunction	
Decreased	5 (11.6%)
Increased	1 (2.3%)
No difference	17 (39.5%)
Impact on Length of Stay	
Decreased	5 (11.6%)
Increased	1 (2.3%)
No difference	17 (39.5%)
JADAD score	

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-2	1 (2.0%)
-1	2 (4.0%)
0	1 (2.0%)
1	3 (6.0%)
2	2 (4.0%)
3	1 (2.0%)
5	2 (4.0%)
6	1 (2.0%)
GRADE Level of Evidence	
High	3 (6.0%)
Moderate	19 (38.0%)
Low	18 (36.0%)
Very Low	10 (20.0%)
Selection bias	
No	6 (14.0%)
Unclear	1 (2.3%)
Yes	5 (11.6%)
Allocation concealment bias	
No	6 (14.0%)
Unclear	4 (9.3%)
Yes	2 (4.7%)
Performance bias	
No	5 (11.6%)
Yes	7 (16.3%)
Detection bias	
No	4 (9.3%)
Yes	8 (18.6%)
Attrition bias	
No	6 (14.0%)
Unclear	3 (7.0%)
Yes	3 (7.0%)

RCT= randomized controlled trial, SD=standard deviation, LT=liver transplantation, LDLT=living donor liver transplantation,

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Table 2. ERAS Item	Summary	Evidence Level	Grade of recommendation
1 PREOPERATIVE COUNSELING	Patients on waiting list should receive dedicated, multidisciplinary educational counselling.[47,48]	Low	Strong
2 PREHABILITATION	***Adapted Physical therapy*** There is no evidence yet of the benefit or harm of physical exercise in cirrhotic patients before liver transplantation.[49,50]	Low	Weak
	Preoperative nutritional screening Patients with cirrhosis should be screened for malnutrition, using a validated tool, and addressed to a multidisciplinary team for nutritional intervention.[51,52]	Moderate	Strong
	Preoperative nutrition cirrhotic patients malnourished or in the preoperative period should receive 30-35 Kcal x kg^{-1} x d^{-1} and a protein intake of 1.5 g x kg^{-1} x d^{-1}, through a standard nutrition regimen minimizing periods of starvation, with no need of protein restriction in case of HE.[51]	High	Strong
	Probiotics Some evidence supports the use of probiotics, prior to, or on the day of liver transplantation. The duration of the treatment and the number of strains included are variable across the studies.[53,54]	High	Weak
	Preoperative immunonutrition the available evidence is nonconclusive, and no recommendation can be given for systematic IN before LT.[55]	High	Weak
3 PERIOPERATIVE FASTING AND CARBOHYDRATE LOADING	***Preoperative fasting*** Preoperative fasting does not need to exceed 6 h for solids and 2 h for liquids. Caution should be considered in case of risk factors for delayed gastric emptying (tense ascites, diabetes or autonomic dysfunction).[5,51]	Low	Strong
	Carbohydrate loading Carbohydrate loading may be recommended at patient admission for liver transplantation, at least 2 h before induction of anaesthesia.[5,56] Caution should be considered in case of risk factors for delayed gastric emptying (tense ascites, diabetes or autonomic dysfunction).	Low	Weak
4 ANTIMICROBIAL PROPHYLAXIS	It is recommended to administer antibiotic prophylaxis only during the intraoperative period. Extending the duration of prophylaxis does not provide any advantages. Systematic selective digestive decontamination is not recommended.[57,58]	Moderate	Strong
5 ANTITHROMBOTIC PROPHYLAXIS	***Antithrombotic prophylaxis*** There is no evidence in favour or against thrombotic prophylaxis, but compressive stockings and intermittent pneumatic compression devices during LT may be recommended.	Very Low	Weak
	Anticoagulation prophylaxis There is insufficient evidence to provide any formal recommendation on antiaggregation or anticoagulation. When available, the viscoelastic coagulation monitoring may be used to guide the therapeutic decision.	Very Low	Weak
6 ANESTHETIC PREMEDICATION	Long-acting anxiolytic drugs should be avoided. Dose-adjusted, short-acting anxiolytics may be considered in selected patients.	Very Low	Weak
7 INCISION	The choice of incision is at the surgeon's discretion, depending on the graft and patient's morphology. Mercedes-type incision may probably be avoided due to higher risk of incisional hernia.	Low	Weak
8 TEMPORARY PORTOCAVAL SHUNT	The available evidence suggest that the use of temporary porto-caval surgical shunt may be beneficial in reducing the red blood cell transfusion requirement, length of stay, PNF and mortality rates.[59,60] Its use is however submitted to the surgeon and anaesthesiologist's decision during surgery.	Low	Weak
9 SHORT ACTING ANESTHETIC PROTOCOL	Short acting anesthetics can be considered in LT, and within anesthetic gases, little evidence suggest that sevoflurane may be preferred to desflurane.[61] Cerebral or nociception monitoring anesthetic titration may be critically used. Neuromuscular monitoring should guide the appropriate level of muscle relaxation and reversal.	Low	Strong
10 PERIOPERATIVE ANALGESIA	We recommend using multimodal and balanced analgesia to manage perioperative analgesia after LT. There is not enough published evidence to state in favor or against an opioid-sparing management: PCA-based morphine may be considered, with caution among patients at high risk for delirium. TAP block may be considered, while TEA cannot be recommended after LT.[62,63]	Low	Strong
11 EARLY EXTUBATION	Each patient undergoing LT should be screened for eligibility to early extubation (< 3-8h).[64] The eligibility should rely on published scores and on local policies and organization for postoperative monitoring.[65,66]	Low	Strong
12 ABDOMINAL DRAINAGE	There is insufficient evidence to recommend no routine drain policy in liver transplantation.[67] Whenever a drain is used, it may be advisable to remove as soon as possible. It can be considered to systematically drain the peritoneal cavity of patients affected by refractory ascites.	Low	Weak
13 FLUID MANAGEMENT	A restrictive fluid management strategy may carefully be considered during LT over a more liberal one.[68] Indirect evidence from other major surgery population suggest that a goal-directed fluid therapy may provide better outcomes than standard of care. TEE may be considered to target fluid therapy.	Low	Weak
	Intraoperative blood product management When available, Viscoelastic tests as Thromboelastography (TEG) or Rotational Thromboelastometry (ROTEM) might be used to drive the management of blood products and factor concentrates during LT.[69]	Low	Weak
14 PERIOPERATIVE NORMOTHERMIA	Perioperative normothermia should be maintained during liver transplantation.[70,71]	Low	Strong
15 PROPHYLACTIC NASOGASTRIC PROBE	Indirect evidence suggest that routine postoperative nasogastric probe after liver transplantation is not indicated. Nasogastric tubes placed during surgery should be removed before reversal of anaesthesia.	Low	Strong
16 POSTOPERATIVE NAUSEA AND VOMITING	Indirect evidence suggest the use of a multimodal approach to PONV, with 2 antiemetic drugs as prophylaxis (e.g. 5-HT3 antagonist and steroids).	Low	Strong
17 EARLY ORAL NUTRITION	Normal food oral intake and/or enteral nutrition (nasogastric tube or jejunostomy) should be started 12-24h after liver transplantation, according to patient's tolerance. Parenteral nutrition should be considered as the very last option, when the use of oral route (enteral feeding tubes or jejunostomy) is not possible.[51]	Very Low	Strong
	Nutritional supplements There is no clear evidence of the benefit of nutritional supplements after liver transplantation.[72,73]	Low	Weak
18 EARLY MOBILISATION	Early mobilization after LT should be encouraged with early-goal directed interventions, from the morning after LT until hospital discharge.[75,76] Physical rehabilitation may be continued after discharge.	Moderate	Strong

ACCEPTED

19 GLYCEMIC CONTROL	We recommend a protocolized approach to blood glucose management in LT patients targeting an upper blood glucose level ≤180 mg/dL from the intraoperative period to the early postoperative period (first 24-48 hours postoperatively in the absence of complications and/or organ failure).[77–80]	Moderate	Strong
20 POSTOPERATIVE ILEUS	There are no acknowledged strategies to prevent postoperative ileus after LT.	Low	Weak
21 POSTOPERATIVE EDUCATION	Systematic educational programs after liver transplantation may increase patient awareness and knowledge on the immunosuppressive therapy and on physical changes after LT. Such multidisciplinary programs could include a clinical pharmacist, and should be continued over a long period after liver transplantation.[80-82]	Low	Strong
22 AUDIT	Systematic audit improves compliance and clinical outcome in healthcare practice.[2,4,5]	Moderate	Strong

LT=liver transplantation, Kcal=kilocalories, IN=immunonutrition, h=hours

Figure 1

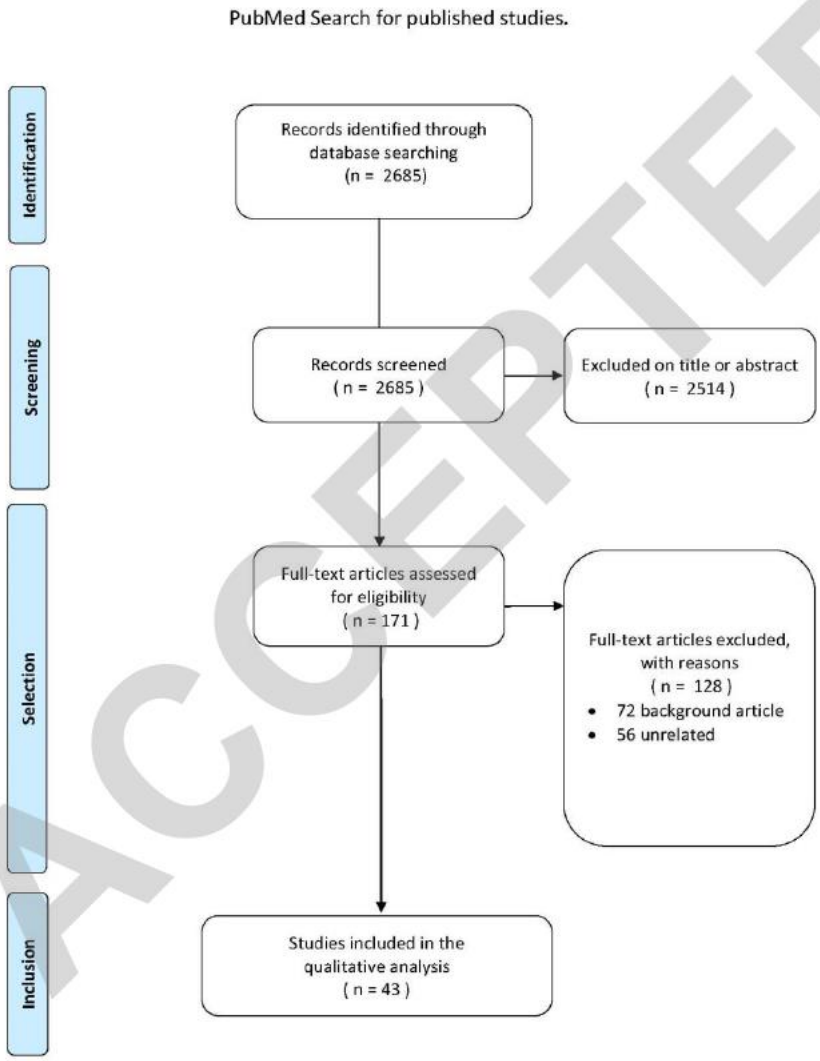

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Figure 2

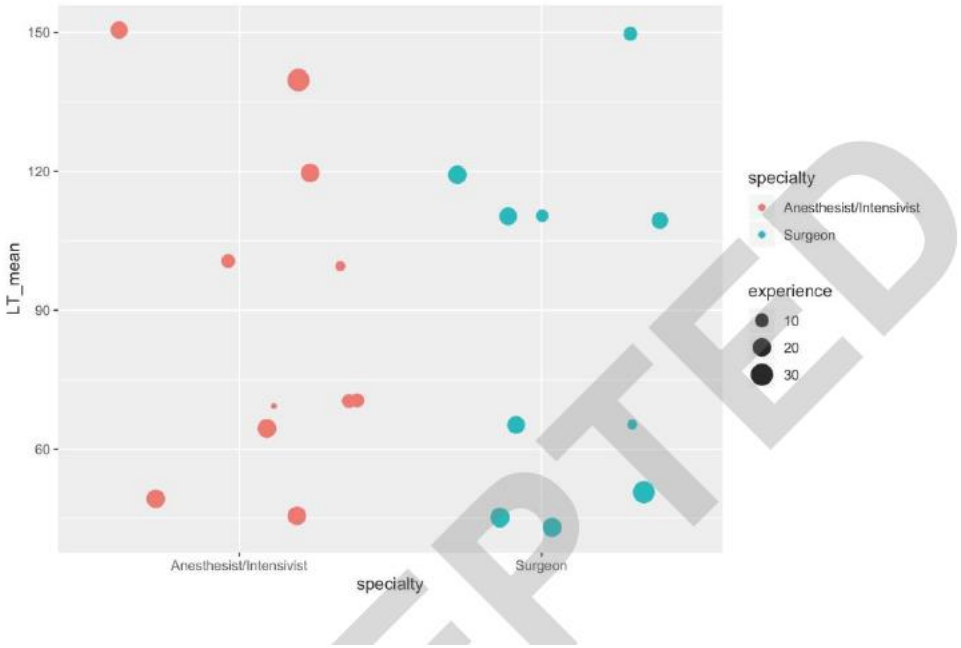
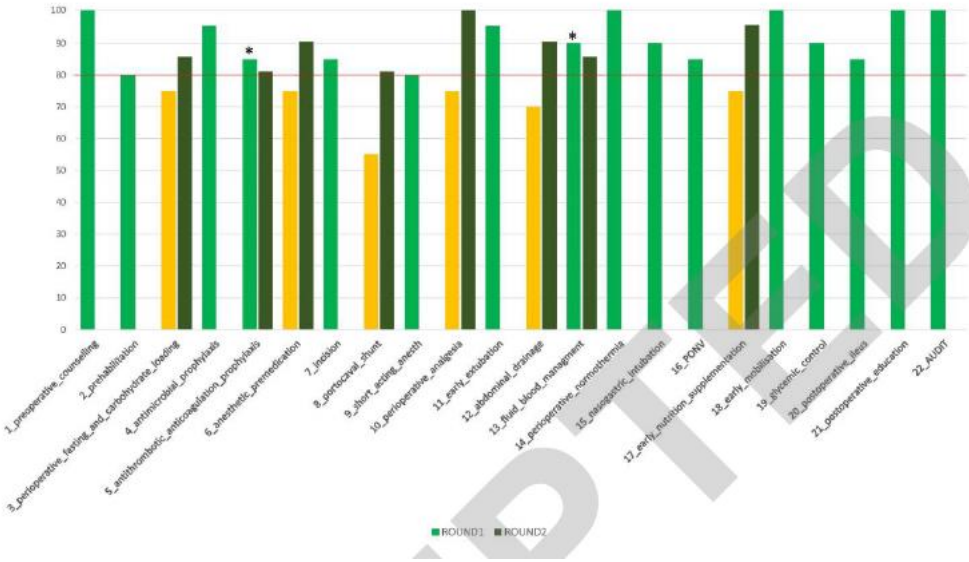


Figure 3



9 RESUME – ABSTRACT

La transplantation hépatique (TH) est le traitement de référence de la cirrhose et ses complications, à considérer dans son ensemble comme un projet thérapeutique dont le complexe parcours de soins nécessite une mobilisation importante de ressources humaines et financières. Le concept du programme de Récupération Améliorée après Chirurgie (RAC ou Enhanced Recovery After Sugery-ERAS) est un protocole de soins visant à réduire le stress chirurgical, d'améliorer la récupération, de réduire le taux de complications post-opératoires et la durée moyenne de séjour (DMS). L'ensemble de ce travail de recherche repose sur l'hypothèse qu'un protocole de RAC appliqué à la TH pourrait simplifier la prise en charge des malades tout en améliorant les suites post-opératoires et en diminuant la durée de leur récupération fonctionnelle. Une première étude prospective sur un échantillon restreint de malades transplantés hépatiques et bénéficiant d'une prise en charge RAC a montré la sécurité et la faisabilité d'un tel programme avec un taux d'adhésion de 72.9% au protocole, ainsi qu'une réduction significative de 47% de la durée totale d'hospitalisation. Compte tenu de l'absence de critères de jugement (CdJ) de RAC en TH, il a fallu les construire en trois études: les deux premières ont permis de déterminer les CdJ en TH (morbidité, suivi de mortalité, dysfonction du greffon, récupération, durée de séjour), et de RAC en chirurgie hépatique (durée d'hospitalisation, complications, impact économique, durée de récupération fonctionnelle). La dernière étude a permis de définir une liste consensuelle de critères de sortie après transplantation hépatique, définissant la récupération fonctionnelle. L'originalité de cette récupération repose sur le fait qu'elle s'applique au malade et au greffon avec des critères pour chacun. La dernière étape a consisté en la réalisation des recommandations officielles de la RAC en transplantation hépatique, sous l'égide de la société ERAS, sur la base de la littérature existante. Une révision systématique de la littérature (PROSPERO CRD42019132798) et un consensus via 27 experts internationaux issus de 12 centres de greffe, ont permis la rédaction de la première édition des recommandations. Tout au long de ce travail de recherche, il a été mis en évidence que la RAC en TH est faisable et sûre, et que parmi les critères de jugement les plus pertinents, la durée de récupération fonctionnelle était le plus appropriée. La définition des recommandations permettra une diffusion standardisée de l'impact de la RAC en TH, avec la récupération fonctionnelle comme critère de jugement à la clé.

MOTS CLES : Récupération améliorée après chirurgie ; RAC ; Transplantation Hépatique ; Delphi ;

Liver transplantation (LT) is the reference treatment for cirrhosis and its complications, to be considered as a complex therapeutic project requiring a significant mobilization of human and financial resources. The Enhanced Recovery After Surgery (ERAS) program is a protocol of care aiming at reducing surgical stress, improving recovery, reducing the rate of post-operative complications and the length of hospital stay. All of this research work is based on the hypothesis that an ERAS protocol in LT could simplify the management of patients while improving recovery and reducing the length of their functional recovery. A first prospective study on a small sample of patients undergoing LT with an ERAS program showed the safety and feasibility of such a program with a compliance rate of 72.9% to the protocol, as well as a significant reduction of the hospital stay. Given the absence of endpoints for ERAS in LT, we had to build them with the three following studies: the first two defined the common endpoints in LT (morbidity, mortality, graft dysfunction, recovery , length of stay), and in ERAS and hepatic surgery (length of stay, complications, economic impact, duration of functional recovery). The third study allowed to define a consensual list of discharge criteria after liver transplantation, defining functional recovery. The originality of this recovery is based on the fact that applies to the patient and to the graft with dedicated criteria. The last step consisted in the realization of the official ERAS recommendations in liver transplantation, on the basis of the existing literature. A systematic review of the literature (PROSPERO CRD42019132798) and a consensus via 27 international experts from 12 transplant centers, enabled the drafting of the first edition of the recommendations. Throughout this research, we showed how ERAS in LT feasible and safe, and that among the most relevant endpoints, the duration of functional recovery is the most appropriate. The definition of these recommendations will allow a standardized dissemination of the impact of ERAS in LT, with functional recovery as an endpoint.

KEY WORDS; Enhanced recovery after surgery; ERAS; Liver Transplantation; Delphi;