第2回　肝臓移植の基準等に関する作業班

議事次第

日時：平成22年11月4日（木）
17：00～19：00
場所：厚生労働省　共用第6会議室

1. 開　会
2. 議　事
（1）　改正法施行後の状況について
（2）　肝臓提供者（ドナー）適応基準について
（3）　レシピエント選択基準について
（4）　その他
3. 閉　会

〈配布資料〉
資料1－1　臓器の移植に関する法律の一部を改正する法律（平成 21 年法律第 83 号）の概要
資料1－2　臓器の移植に関する法律施行規則の一部を改正する省令について（概要）
資料1－3「臓器の移植に関する法律の運用に関する指針（ガイドライン）の一部改正」
について（概要）
資料1－4　改正法施行後の脳死下提供事例一覧
資料2　　肝臓提供者（ドナー）適応基準　改正（案）
資料3　　レシピエント選択基準について

参考資料1　肝臓提供者（ドナー）適応基準
参考資料2　HBc 抗体陽性ドナーに関する文献　2 報　（國土班員提出資料）
参考資料3　肝臓移植希望者（レシピエント）選択基準
参考資料4　肝臓移植希望待機患者概要　小腸移植希望待機患者一覧
参考資料5　脳死肝移植　適応要件の変更について　（猪股班員提出資料）
参考資料6　分割肝移植について
参考資料7　分割肝、体重差に関するレシピエント選択について（上本班員提出資料）
参考資料8　小腸移植希望者（レシピエント）選択基準
参考資料9　適応評価後の予後について（梅下班員提出資料）

資料１－１

臓器の移植に関する法律の一部を改正する法律（平成21年法律第83号）の概要

１　臓器摘出の要件の改正

移植術に使用するために臓器を摘出することができる場合を次の①又は②のいずれかの場合とする。

① 本人の書面による臓器提供の意思表示があった場合であって、遺族がこれを拒まないとき又は遺族がないとき（現行法での要件）。

② 本人の臓器提供の意思が不明の場合であって、遺族がこれを書面により承諾するとき。

２　臓器摘出に係る脳死判定の要件の改正

移植に係る脳死判定を行うことができる場合を次の①又は②のいずれかの場合とする。

① 本人が

Ａ 書面により臓器提供の意思表示をし、かつ、

Ｂ 脳死判定の拒否の意思表示をしている場合以外の場合

であって、家族が脳死判定を拒まないとき又は家族がないとき。

② 本人について

Ａ 臓器提供の意思が不明であり、かつ、

Ｂ 脳死判定の拒否の意思表示をしている場合以外の場合

であって、家族が脳死判定を行うことを書面により承諾するとき。

３　親族への優先提供

臓器提供の意思表示に併せて、書面により親族への臓器の優先提供の意思を表示することができることとする。

４　普及・啓発

国及び地方公共団体は、移植術に使用されるための臓器を死亡した後に提供する意思の有無を運転免許証及び医療保険の被保険者証等に記載することができることとする等、移植医療に関する啓発及び知識の普及に必要な施策を講ずるものとする。

５　検討

政府は、虐待を受けた児童が死亡した場合に当該児童から臓器が提供されることのないよう、移植医療に従事する者が児童に対し虐待が行われた疑いがあるかどうかを確認し、及びその疑いがある場合に適切に対応するための方策に関し検討を加え、その結果に基づいて必要な措置を講ずるものとする。

資料１－２

臓器の移植に関する法律施行規則の一部を改正する省令について（概要）

１　改正の内容

① 臓器の移植に関する法律（平成９年法律第104号。以下「法」という。）の改正により、１５歳未満の者からの臓器提供が可能となることから、小児（６歳未満の者）に係る脳死判定基準について定めること。

（改正箇所：臓器の移植に関する法律施行規則（平成９年厚生省令第78号。以下「施行規則」という。）第２条）

② 法の改正により、臓器提供に係る本人意思が不明な場合に、家族の書面による承諾により脳死判定・臓器摘出が可能となること等から、脳死判定及び臓器摘出に関する記録について規定の整備を行うこと。

（改正箇所：施行規則第５条及び第６条）

③ 法の改正により、法附則第４条が削除されることに伴い、規定の整理を行うこと。

（改正箇所：施行規則附則第３条及び第４条）

２　根拠規定

法第６条第４項及び第１０条第１項

３　施行日

平成２２年７月１７日

資料１－３

「臓器の移植に関する法律の運用に関する指針（ガイドライン）の一部改正」について（概要）

Ⅰ　改正の内容

１　臓器提供に係る意思表示等に関する事項

（１）臓器を提供しない意思表示等について

臓器を提供する意思がないこと又は法に基づく脳死判定に従う意思がないことが表示されていた場合には、年齢に関わらず、臓器を提供する意思がないことを表示した者からの臓器摘出及び法に基づく脳死判定に従う意思がないことを表示した者に対する法に基づく脳死判定は行わないこと。

（２）知的障害者等の意思表示について

主治医等が家族等に対して病状や治療方針の説明を行う中で、患者が知的障害者等の臓器提供に関する有効な意思表示が困難となる障害を有する者であることが判明した場合においては、年齢に関わらず、当面、その者からの臓器摘出は見合わせること。

２　遺族及び家族の範囲に関する事項

臓器の摘出の承諾に関して法に規定する「遺族」の範囲については、現行ガイドラインで定める範囲を維持するが、死亡した者が未成年であった場合には、特に父母それぞれの意向を慎重かつ丁寧に把握すること。

３　小児からの臓器提供施設に関する事項

①　救急医療等の関連分野において、高度の医療を行う施設であること

②　虐待防止委員会等の虐待を受けた児童への対応のために必要な院内体制が整備されていること

を要件とし、現行ガイドラインで定める４類型に、日本小児総合医療施設協議会の会員施設を加える。

・大学附属病院

・日本救急医学会の指導医指定施設

・日本脳神経外科学会の専門医訓練施設（Ａ項）

（注）Ａ項とは、専門医訓練施設のうち、指導に当たる医師、症例数等において特に充実した施設。

・救命救急センターとして認定された施設

・日本小児総合医療施設協議会の会員施設

４　虐待を受けた児童への対応等に関する事項

（１）　児童からの臓器提供を行う施設に必要な体制

①　虐待防止委員会等の虐待を受けた児童への対応のために必要な院内体制が整備されていること。

②　児童虐待の対応に関するマニュアル等が整備されていること。なお、当該マニュアルは、新たな知見の集積により更新される必要があること。

（２）　虐待が行われた疑いの有無の確認について

①　虐待の徴候が確認された場合には、児童からの臓器提供を行う施設においては、虐待対応のための院内体制の下で、虐待が行われた疑いがあるかどうかを確認すること。

② この結果、当該児童について虐待が行われた疑いがあると判断した場合には、児童相談所等へ通告するとともに、警察署へ連絡するなど関係機関と連携し、院内体制の下で当該児童への虐待対応を継続すること。

③ その後、医学的理由により当該児童について虐待が行われたとの疑いが否定された場合についても、その旨を関係機関に連絡した上で、当該児童への虐待対応の継続の要否について検討すること。

（3） 臓器提供を行う場合の対応

① 主治医等が家族に対し、臓器提供の機会があること等を告げようとする場合には、事前に、虐待防止委員会の委員等と情報共有を図り、必要に応じて助言を得ること。

② 児童から臓器の摘出を行う場合には、施設内の倫理委員会等の委員会において、２及び３（１）の手続きを経ていることを確認し、その可否を判断すること。

③ 施設内の倫理委員会等で、児童について虐待が行われた疑いがなく当該児童からの臓器摘出が可能と判断した場合であっても、検視等の手続が行われる場合には、捜査機関との連携を十分に図ること。

5 脳死した者の身体から臓器を摘出する場合の脳死判定を行うまでの標準的な手順に関する事項

主治医等が、患者の状態について、法に規定する脳死判定を行ったとしたならば、脳死とされうる状態にあると判断した場合（臓器の移植に関する法律施行規則（平成９年厚生省令第７８号。以下「施行規則」という。）第２条第１項に該当すると認められる者（同項各号のいずれかに該当する者を除く。）について、同条第２項各号の項目のうち第１号から第４号までのいずれもが確認された場合。）以後において、家族等の脳死についての理解の状況等を踏まえ、臓器提供の機会があること、及び承諾に係る手続に際しては主治医以外の者（臓器移植ネットワーク等の臓器のあっせんに係る連絡調整を行う者（以下「コーディネーター」という。）による説明があることを口頭又は書面により告げること。

6 臓器摘出に係る脳死判定に関する事項

法に規定する脳死判定の具体的な方法については、施行規則において定められているところであるが、さらに個々の検査の手法については、「法的脳死判定マニュアル」（厚生科学研究費特別研究事業「脳死判定手順に関する研究班」平成１１年度報告書）に準拠して行うこと。

ただし、脳幹反射消失の確認のうち、鼓膜損傷がある症例における前庭反射の確認については年齢に関わらず、平坦脳波の確認における基本条件等及び無呼吸テストの基本条件等については６歳未満の者の場合において、「小児の脳死判定及び臓器提供等に関する調査研究」（平成２１年度報告書）の該当部分に準拠して行うこと。

7 その他

脳死判定・臓器摘出の要件変更に伴う、関係規定の整備を行うこと。

Ⅱ 根拠規定 臓器の移植に関する法律

Ⅲ 施行日 平成２２年７月１７日

改正法施行後の脳死下での臓器提供事例について(平成22年11月4日現在)

脳死判定事例(提供事例)	提供日	原疾患	提供施設	書面による意思表示	心臓	肺	肝臓	膵臓	腎臓	小腸	眼球
第88例目(第87例目)	平成22年8月10日	20代♂交通外傷	関東甲信越	なし	国立循環器病研究センター	岡山大(両肺)	東大 —	藤田保健衛生大(膵腎同時)	群馬大	—	東京歯科大学市川総合病院 東京歯科大学市川総合病院
第89例目(第88例目)	平成22年8月19日	♂	近畿	なし	東大	阪大(両肺)	京大 —	名古屋第二赤十字(膵腎同時)	神戸大	—	— —
第90例目(第89例目)	平成22年8月22日	50代♀脳血管障害	東海	なし	東北大	東北大(両肺)	阪大 —	名古屋第二赤十字(膵腎同時)	藤田保健衛生大	—	名古屋大 藤田保健衛生大
第91例目(第90例目)	平成22年8月27日	40代♀くも膜下出血	松山赤十字病院	あり	—	—	北海道大 —	東京女子医大(膵腎同時)	愛媛県立中央病院	—	愛媛大 愛媛大
第92例目(第91例目)	平成22年8月29日	40代♂蘇生後脳症	関東甲信越	なし	—	京大 京大	国立成育医療研究センター 京大	九州大(膵腎同時)	千葉大	東北大	東京歯科大学市川総合病院 東京歯科大学市川総合病院
第93例目(第92例目)	平成22年9月2日	40代♀くも膜下出血	北部九州	なし	国立循環器病研究センター	東北大(両肺)	名古屋大 —	—	東京女子医大 長崎医療センター	東北大	— —
第94例目(第93例目)	平成22年9月4日	成人♂頭部外傷	東北	なし	東京女子医大	岡山大 京大	名古屋大 —	藤田保健衛生大 福島県立医大	福島県立医大	九州大	— —
第95例目(第94例目)	平成22年9月7日	成人♂蘇生後脳症	関東甲信越	なし	国立循環器病研究センター	福岡大 —	北海道大 —	東京女子医大(膵腎同時)	長野赤十字	—	長野赤十字 長野赤十字
第96例目(第95例目)	平成22年9月12日	40代♂心疾患	市立札幌病院	なし	—	岡山大(両肺)	東大 —	藤田保健衛生大(膵腎同時)	市立札幌	—	— —
第97例目(第96例目)	平成22年9月18日	30代♂	近畿	なし	国立循環器病研究センター	—	京大 岡山大	阪大(膵腎同時)	近江八幡市立総合医療センター	—	— —
第98例目(第97例目)	平成22年9月25日	70代♂脳幹梗塞	北部九州	なし	—	—	— —	—	熊本赤十字 熊本赤十字	—	— —
第99例目(第98例目)	平成22年9月27日	50代♂脳血管障害	北海道	なし	埼玉医科大学国際医療センター	東北大 福岡大	京大 —	—	北海道大 市立札幌	—	— —
第100例目(第99例目)	平成22年9月30日	50代♀くも膜下出血	市立札幌病院	なし	阪大	東北大	京大 —	東北大(膵腎同時)	札幌北楡	—	— —
第101例目(第100例目)	平成22年9月30日	30代♂蘇生後脳症	東北大学病院	なし	国立循環器病研究センター	—	京大 —	阪大(膵腎同時)	仙台社会保険	—	東北大 東北大
第102例目(第101例目)	平成22年10月3日	70代♀脳出血	関東	なし	—	—	岡山大 —	—	東邦大医療センター大森病院 東京女子医大	—	— —
第103例目(第102例目)	平成22年10月13日	18歳以上♂脳血管障害	西日本	なし	—	—	阪大 —	東京女子医大(膵腎同時)	日赤和歌山医療センター	—	— —
第104例目(第103例目)	平成22年11月3日	30代♀くも膜下出血	九州大学病院	なし	阪大	岡山大(両肺)	広島大 —	藤田保健衛生大(膵腎同時)	福岡赤十字	—	— —

資料２

＜肝臓＞臓器提供者（ドナー）適応基準（案）

１．以下の疾患又は状態を伴わないこととする。

（１）全身性の活動性感染症

（２）ＨＩＶ抗体、ＨＴＬＶ－１抗体、ＨＢｓ抗原などが陽性

（３）クロイツフェルト・ヤコブ病及びその疑い

（４）悪性腫瘍（原発性脳腫瘍及び治癒したと考えられるものを除く。）

２．以下の疾患又は状態を伴う場合は、慎重に適応を決定する。

（１）病理組織学的な肝臓の異常

（２）生化学的肝機能検査の異常

（３）１週間以内の腹部、消化管手術及び細菌感染を伴う腹部外傷

（４）胆道系手術の既往

~~（５）重度糖尿病~~

~~（６）過度の肥満~~

~~（７）重度の熱傷~~

（５）長期の低酸素状態

（６）高度の高血圧又は長期の低血圧

（７）ＨＣＶ抗体陽性

（８）ＨＢｃ抗体陽性

（９）先天性の代謝性肝疾患の保有の可能性がある者

（１０）重度糖尿病、過度の肥満、重症熱傷、その他の重度の全身性疾患

備考）摘出されたドナー肝については、移植前に肉眼的、組織学的に観察し、最終的に適応を検討することが望ましい(移植担当医の判断に委ねる)。

付記　上記の基準は適宜見直されること。

資料３

「肝臓移植希望者（レシピエント）選択基準」について

１．　乳幼児レシピエントについて

- 血液型不適合移植を可能とする場合、年齢は何歳までが適当か。
- 時間的問題はないか。

２．　分割肝移植について

- 現在は第１レシピエント候補の移植施設が分割肝の可否を判断した後に下位のレシピエントに係る施設に分割肝の意思確認を行っている。（参考資料６参照）

３．　肝小腸同時移植について

（１）背景

肝小腸同時移植希望者については、現在、登録者はいないが、今後、改正法施行に伴い、肝小腸同時移植希望の登録者の増加が予想されることから、平成 21 年 12 月に開催された、小腸移植の基準等に関する作業班においても、肝小腸同時移植希望者の取り扱いについて、その議論が必要との意見があった。

（２）小腸移植実績

脳死下小腸移植 (1996－2010. 9)	９名 （うち生体肝移植既実施者数２名）
生体小腸移植 (1996-2009)	１１名 （うち肝小腸同時移植者１名）

臓器移植ネットワーク移植施設会議資料より(2010. 6. 5)

（３）肝小腸同時移植希望者の取り扱い（案）

① 肝小腸同時移植希望者が肝臓のリストで１位となった場合

小腸リストでの順位にかかわらず、肝臓と小腸を移植する。（但し、小腸レシピエント１位の者が親族優先提供に関わる者の場合はこの限りではない）

② 肝小腸同時移植希望者が小腸リストで１位になった場合

１：　親族優先

２：　肝臓の医学的緊急度　９点

３：　肝臓の医学的緊急度　６点

但し、肝小腸同時移植希望者に関しては小腸適応で status1 または 2 の者は肝臓での医学的緊急度を 6 点とする。

＊緊急度が同点の場合には血液型、待機日数で決定する。

参考資料１

＜肝臓＞臓器提供者（ドナー）適応基準

１．以下の疾患又は状態を伴わないこととする。

（１）全身性の活動性感染症

（２）ＨＩＶ抗体、ＨＴＬＶ－１抗体、ＨＢｓ抗原などが陽性

（３）クロイツフェルト・ヤコブ病及びその疑い

（４）悪性腫瘍（原発性脳腫瘍及び治癒したと考えられるものを除く。）

２．以下の疾患又は状態を伴う場合は、慎重に適応を決定する。

（１）病理組織学的な肝臓の異常

（２）生化学的肝機能検査の異常

（３）１週間以内の腹部、消化管手術及び細菌感染を伴う腹部外傷

（４）胆道系手術の既往

（５）重症糖尿病

（６）過度の肥満

（７）重症の熱傷

（８）長期の低酸素状態

（９）高度の高血圧又は長期の低血圧

（１０）ＨＣＶ抗体陽性

備考）摘出されたドナー肝については、移植前に肉眼的、組織学的に観察し、最終的に適応を検討することが望ましい(移植担当医の判断に委ねる)。

付記　上記の基準は適宜見直されること。

参考資料2

Review

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Liver grafts from anti-hepatitis B core positive donors: A systematic review

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Background & Aims: Although hepatitis B virus (HBV) transmission after liver transplantation of grafts from HBsAg-negative, anti-HBc positive donors is well established, the growing organ shortage favours the use of such marginal grafts. We systematically evaluated the risk of HBV infection after liver transplantation with such grafts and the effect of anti-HBV prophylaxis.

Methods: We performed a literature review over the last 15 years identifying 39 studies including 903 recipients of anti-HBc positive liver grafts.

Results: Recurrent HBV infection developed in 11% of HBsAg-positive liver transplant recipients of anti-HBc positive grafts, while survival was similar (67–100%) to HBsAg-positive recipients of anti-HBc negative grafts. *De novo* HBV infection developed in 19% of HBsAg-negative recipients being less frequent in anti-HBc/anti-HBs positive than HBV naive cases without prophylaxis (15% vs 48%, $p < 0.001$). Anti-HBV prophylaxis reduced *de novo* infection rates in both anti-HBc/anti-HBs positive (3%) and HBV naive recipients (12%). *De novo* infection rates were 19%, 2.6% and 2.8% in HBsAg-negative recipients under hepatitis B immunoglobulin, lamivudine and their combination, respectively.

Conclusions: Liver grafts from anti-HBc positive donors can be safely used, preferentially in HBsAg-positive or anti-HBc/anti-HBs positive recipients. HBsAg-negative recipients should receive prophylaxis with lamivudine, while both anti-HBc and anti-HBs positive recipients may need no prophylaxis at all.

Introduction

despite the recent advances in liver transplantation (LT), there is a growing gap between the availability of donors and recipients on the waiting list. One of the current efforts to overcome the organ shortage is based on the use of grafts that are from donors with antibodies against the HBV core antigen (anti-HBc), but hepatitis B surface antigen (HBsAg) negative; the so called "anti-HBc positive donors" [1]. These grafts are rather common in countries with high or even intermediate prevalence of HBV infection, such as Asia and the Mediterranean basin. However, anti-HBc positive liver donors frequently have occult HBV infection, i.e. persistent liver and/or serum HBV DNA without serologic evidence of active HBV infection (negative HBsAg with or without positive anti-HBs). Indeed, several studies in HBsAg-negative subjects have shown that there is often the detection in the liver of covalently closed circular DNA (cccDNA) and pregenomic RNA, which is a marker of ongoing viral replication [2,3], and that may significantly increase with the use of post-LT immunosuppression and in particular with corticosteroids [4]. The liver grafts from anti-HBc positive donors are currently the main sources of *de novo* HBV infection after LT [5,6], which is usually defined by the development of positive HBsAg and/or detectable serum or liver HBV DNA in previously HBsAg recipients or even development of positive anti-HBc in previously HBV naive recipients. However, the literature documenting the risk of *de novo* HBV infection and the effects on the graft is scanty and conflicting.

The lack of definite data explains the wide variation in current clinical practice. In a survey in the USA in 2001, almost half of liver transplant physicians reported that they did not use anti-HBc positive donors in HBV naive recipients [7]. In a more recent international survey, the responders documented using prophylaxis with a nucleos(t)ide analogue (mostly lamivudine, but also entecavir and adefovir) in the majority of LT recipients of anti-HBc positive grafts, and 61% also used hepatitis B immunoglobulin (HBIG) (69% in US and 46% in non-US centres, $p = 0.03$) [8].

In this review, we systematically evaluated all the available data in order to quantify the impact of using liver grafts from anti-HBc positive donors and identify the optimal post-LT prophylaxis. We selected two types of recipients: (a) HBsAg-positive recipients and (b) HBsAg-negative recipients. In particular, we documented the rates of *de novo* HBV infection with or without anti-HBV prophylaxis relative to the donor-recipient HBV serological status, as well as data on the outcome of *de novo* post-LT HBV infection. Our search was based on Medline/PubMed from January 1994 to december 2008 using the search terms "hepatitis B core antibody" and "liver transplantation", in papers published in English. We also conducted a manual search of the reference lists in the review articles. In total, 133 articles were identified. Two authors (E.C., G.V.P.) reviewed the abstracts of these articles to identify potentially relevant articles. In total, 39 original

Keywords: *De novo* HBV infection; Liver transplantation; Marginal donors; Anti-HBc positive donors; Hepatitis B immunoglobulin; Lamivudine; Vaccination.

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Abbreviations: HBV, hepatitis B virus; LT, liver transplantation; anti-HBc, HBV core antigen; HBsAg, hepatitis B surface antigen; cccDNA, covalently closed circular DNA; HBIG, hepatitis B immunoglobulin; LAM, lamivudine.

Table 1. Published studies on the prevalence of anti-HBc positivity among liver donors in different countries.

First author, year [Ref.]	Donors, *n*/*N* anti-HBc		
	Country	Positive/total	Prevalence (%)
Wachs (1995) [42]	USA	25/1190	2
Douglas (1997) [12]	USA	3/332	3
Dodson (1997) [29]	USA	70/2578	3
Shinji (1998) [13]	Japan	16/171	9
Yu (2001) [19]	USA	15/169	9
Nery (2001) [40]	USA	48/724	6
Prieto (2001) [10]	Spain	33/268	12
Lee (2001) [14]	China	16/30	53
Roque-Alfonso (2002) [21]	France	22/315	7
Chen (2002) [16]	Taiwan	24/42	57
Lo (2003) [15]	China	28/51	55

articles evaluated the rate of *de novo* HBV infection from anti-HBc positive donors, were included in the final analysis. Data abstraction was done by one author (E.C.) and any conflicts in data abstraction were arbitrated by discussion with the senior authors (G.V.P., A.K.B.).

Prevalence of anti-HBc positive liver donors

The rate of anti-HBc positivity in liver donors varies substantially in different countries reflecting the local prevalence of HBV infection. Thus, the prevalence of anti-HBc is lower in developed countries ranging from 3% to 15% [9–13], but it may exceed 50% in highly endemic areas [14–16] (Table 1). The prevalence of anti-HBc may also vary in different areas of the same country and in specific ethnic populations (e.g. it is estimated that 25% of non-Hispanic black Americans in the USA are anti-HBc positive) [17], and it is usually higher in older age individuals, who are currently increasingly used as liver donors [10]. The latter could partly explain the increasing number of anti-HBc positive cadaveric livers transplanted in the USA (from 3.9% in 1998 to 4.9% in 2002) [18].

Liver grafts from anti-HBc positive donors to HBsAg-positive recipients

Nine studies [11,19–26] evaluated the recurrence of HBV infection in HBsAg-positive recipients of anti-HBc positive liver grafts (Table 2). During a median follow-up of 27 (19–42) months, post-transplant HBV infection was observed in 12 (10.5%) of 115 recipients, while median survival ranged from 67% to 100%. In the 12 cases with post-transplant HBV infection, the prophylaxis was: three with HBIG, three with lamivudine and six with HBIG and lamivudine (HBIG had been discontinued in one at HBV recurrence). In one retrospective cohort study [20], recipients of anti-HBc positive grafts ($n = 14.5$ with detectable serum HBV DNA at LT) were compared to recipients of anti-HBc negative grafts ($n = 65$). The 14 recipients of anti-HBc positive grafts developed HBV recurrence more frequently (69.2% vs 35.7%, $p = 0.034$) and earlier after LT (2.9 vs 6.4 years, $p < 0.005$). However, the patient and graft survival was not different between the two groups: 60-month survival: 67% vs 68%. In multivariate analysis, HBV recurrence was independently associated with anti-HBc donor status (RR: 2.796, $p = 0.02$) and the use of combined HBIG and lamivudine prophylaxis (RR: 0.249, $p = 0.021$), but not the recipients' pre-transplant HBeAg status [20].

Liver grafts from anti-HBc positive donors to HBsAg-negative recipients–risk of *de novo* HBV infection

We identified 38 relevant studies published as full papers [5,9–13,16,19,21–50] (Table 3). Nine did not have sufficient data regarding the serological HBV status in donors and/or recipients [12,13,23,31,39,43,45,49,50]. Four centres published two studies: one in Spain [36,37] and three in the USA [22,29,30,34,35,40] with two of these reports having overlap in study periods [29,35]. The indication for LT was recorded in 21 studies [10,19, 21–23,25,26,28,30,31,36,37,39,41–45,47,49,50]: HCV cirrhosis was the most common (25%), followed by alcoholic cirrhosis and cholestatic liver diseases. The cohort size ranged from 6 to 91 patients with only two studies reporting >50 patients [26,37]. The total number of patients that could be evaluated was 788.

The diagnosis of *de novo* HBV infection was based on the detection of HBsAg in previously HBsAg-negative recipients with or without compatible biochemical or histological findings in 14 studies [9,10,24,25,27–29,33,35,42,44,45,47,49], or the appearance of HBsAg and/or serum HBV DNA in 19 studies [5,11,13,19, 21,22,26,30–32,34,36–41,43,48]. The presence of HBV DNA was determined by a hybridization technique in three [10,16,37], branched-DNA assay in one [11] and polymerase chain reaction (PCR) assay in the remaining 20 studies [5,9,13,19,21,22,25, 26,28,30–32,34,36,39–41,47–49]. HBV DNA was evaluated in serum in 17 [9–11,16,22,25,26,30,37,39,40,43–45,47–49] and in both serum and liver tissue in nine studies [5,13,19,21,28, 31,32,34,41], while it was also evaluated in leukocytes in two studies [5,34]. In only one study, cccDNA was assessed in liver tissue [36].

Table 2. Published studies of liver transplantation using anti-HBc positive donors in HBsAg-positive recipients.

First author, year [Ref.]	HBsAg positive		Follow-up (months)	HBV recurrence, *n* (%)	Survival (%)
	Recipients, *n*	Anti-HBV prophylaxis			
Yu (2001) [19]	6	HBIG	20	0	100
Manzabeita (2002) [11]	3	HBIG + LAM	26	1 (33)	67
Joya-Varquez (2002) [20]	14	HBIG: 5, LAM: 3, HBIG + LAM: 5	42	9[a] (69)	
Roque-Afonso (2002) [21]	4	HBIG	19	0	75
Nery (2003) [22]	17	LAM: 12, HBIG + LAM: 5	29	0	
Montalti (2004) [23]	26	HBIG ± LAM	NA	0	
Donataccio (2006) [24]	4	HBIG: 3, HBIG + LAM: 1	38	1[b] (25)	100
Pracoso (2006) [25]	5	HBIG + LAM	29	0	67
Celebi-Kobak (2007) [26]	36	HBIG + LAM	19	1 (3)	92

HBIG, hepatitis B immunoglobulin; LAM, lamivudine; NA, not available.

[a] 2/5 patients under HBIG, 3/3 patients under LAM and 4/5 patients under HBIG + LAM.

[b] 1/3 patients under HBIG.

Table 3. Published studies[a] with liver transplantation using anti-HBc positive donors in HBsAg-negative recipients.[b]

First author, year [Ref.]	Anti-HBc (+), anti-HBs (−) recipients				Anti-HBc (+), anti-HBs (+) recipients				HBV naive recipients			
	Patients, *N*	Anti-HBV prophylaxis	Follow-up, months	*De novo* HBV, *n*	Patients, *N*	Anti-HBV prophylaxis	Follow-up, months	*De novo* HBV, *n*	Patients *N*	Anti-HBV prophylaxis	Follow-up, months	*De novo* HBV, *n*
Dickson (1997) [9]	2	None	22	0		None			18	None	22	15
Dodson (1997) [29]	15	None	56	2	7		56	0	25	None	56	18
Dodson (1999) [35]	8	HBIG + LAM	46	0		None			8	HBIG + LAM: 7, HBIG: 1	46	1
Prietro (2001) [10]	3	None	29	0	2	None	29	0	25	None	29	15
Manzabeita (2002) [11]	11	None	26	2	13		26	0	2	HBIG	26	2
Roque-Afonso (2002) [21]	4	HBIG	26	0					12	None: 4, HBIG: 8	22	5
Bacerna (2002) [37]					19	None	NA	0	64		NA	10
Chen (2002) [16]	2	LAM: 1, none: 1	40	0	3	LAM: 2, none:1	40	0	15	LAM: 13, none: 2	40	2
Nery (2003) [22]	13	HBIG + LAM: 4, LAM: 9	22	1	23	HBIG + LAM: 6, none: 17	21	0	8	HBIG + LAM: 2, LAM: 6	37	1
Loss (2003)[1] [32]									11	HBIG (bolus) + LAM + Vaccination	33	0
Suehiro (2005) [28]	4	HBIG + LAM	39	0	3	NA	39	0	15	HBIG + LAM	39	0
De Feo (2005)[2] [27]	NA	None	NA	0	NA	None	NA	0	14	None	NA	6
Donataccio (2006)[3] [24]	NA	HBIG	NA	NA	NA	HBIG	NA	NA	11	HBIG + LAM: 1,	57	7
Umeda (2006) [47]									38	HBIG	42	9
Celebi-Kobak (2007) [26]	4	LAM	17	0	3	LAM	28	0	4	LAM	23	0
Takemura (2007) [33]	2	LAM	31	0	5	HBIG	31	1	9	HBIG	31	1

HBIG, hepatitis B immunoglobulin; LAM, lamivudine; NA, not available.

De novo HBV infection also developed in (a) 1/3 anti-HBs positive recipients under HBIG + LAM + vaccination[1] [32]; (b) 0/35 anti-HBc positive and/or anti-HBs positive recipients under no anti-HBV prophylaxis[2] [27], (c) 0/1 anti-HBc positive recipient (unknown anti-HBs status) under HBIG during 11 months of follow-up[3] [24].

[a] Twenty-two studies with <10 patients each ($n = 13$) [5,19,25,30,34,36,38,40–42,44,46,48] or insufficient data ($n = 9$) on the serological HBV status of donors and/or recipients [12,13,23,31,39,43,45,49,50] are not included. *De novo* HBV infection developed in: (a) 15/57 HBV naive recipients [5,19,25,30,34,38,40–42,48] under no anti-HBV prophylaxis or LAM ± HBIG ± vaccination, (b) 2/51 anti-HBc positive recipients [anti-HBs negative (1/9), anti-HBs positive (1/20), anti-HBs unknown (0/22)] [5,19,25,36,38,40,44,46] under no anti-HBV prophylaxis or HBIG ± LAM ± vaccination and (d) 1/25 only anti-HBs positive recipients under LAM plus vaccination [44]. *De novo* HBV infection also developed in (a) 15/20 anti-HBc positive recipients (unknown anti-HBs status) under no anti-HBV prophylaxis (15/16) [13] or HBIG + LAM (0/1) [31] or HBIG plus vaccination (0/3) [49], (b) 0/11 anti-HBs positive recipients under HBIG plus vaccination [49] and (c) 14/95 recipients with unknown anti-HBs/anti-HBc status under HBIG ± LAM or no prophylaxis (9/67) [12,23,39,43] or HBIG ± vaccination (2/25) [45,50] or vaccination alone (3/3) [50].

[b] Thirty one recipients (from seven studies [11,16,21,22,24,36,37]) with successful pre-LT vaccination and no post-LT prophylaxis were not included; three (9.6%) of them developed *De novo* HBV infection. In addition, 34 recipients (from seven studies [19,24–26,31,33,34]) with successful pre-LT vaccination and HBIG and/or lamivudine post-LT prophylaxis were not included; none of them developed *de novo* HBV infection.

The immunosuppressive therapy after LT was reported in detail for each patient in only one study [32], while the immunosuppressive regimens with or without the number of patients in each regimen was reported in 19 studies [10,11,13,16,19,25,28,30,31,33,34,36,39,43–45,47–49] and no information on the immunosuppression was provided in 18 studies [5,9,12,21–24,26,27,29,35,37,38,40–42,46,50]. Tacrolimus or cyclosporine-based regimens were used in seven [10,11,25,28,34,36,39], only tacrolimus-based regimens in 10 [13,19,31–33,43,45,47–49] and only cyclosporine-based regimens in three studies [16,30,44]. In 18 studies [11,13,16,19,25,28,30–34,36,43–45,47–49] steroids were used as immunosuppressive regimen, while in two studies [10,39] steroid use was not reported. The plan of steroid withdrawal (usually tapered and stopped 3–12 months after LT) was only reported in 10 studies [16,19,31,32,34,44,45,47–49].

In total, *de novo* HBV infection was observed in 149 (18.9%) of 788 recipients at a median of 24 (5–54) months after LT. Post-transplant anti-HBV prophylaxis significantly affected the probability of *de novo* HBV infection, which developed in 28.2% (119/422) of recipients without, and 8.2% (30/366) of recipients with post-transplant prophylaxis ($p < 0.001$). Moreover, *de novo* HBV infection developed more rapidly in patients without than with post-transplant prophylaxis: median onset after LT: 19 vs 35 months ($p = 0.05$).

Probability of de novo HBV infection without post-transplant anti-HBV prophylaxis

De novo HBV infection after LT with grafts from anti-HBc positive donors developed in 47.8% (89/186) of HBV naive recipients compared to 15.2% (21/138) of recipients with serological markers of past HBV infection ($p < 0.001$) or 9.7% (3/31) of recipients with successful pre-LT vaccination ($p < 0.001$). *De novo* HBV infection also developed in 8.9% (6/67) of HBsAg-negative recipients with unknown pre-LT HBV status. The presence of anti-HBs in anti-HBc positive recipients, which was reported in 106 of 138 such cases, reduced the probability of *de novo* HBV infection but did not eliminate it (Fig. 1).

Anti-HBc positive liver grafts to HBsAg-negative recipients with past HBV infection. (a) HBsAg and anti-HBs negativity with anti-HBc positivity in recipients. In eight studies [5,9–11,16,29,36,38], *de novo* HBV infection developed in 13.1% (5/38) of such recipients with anti-HBc positive donors during a median follow-up of

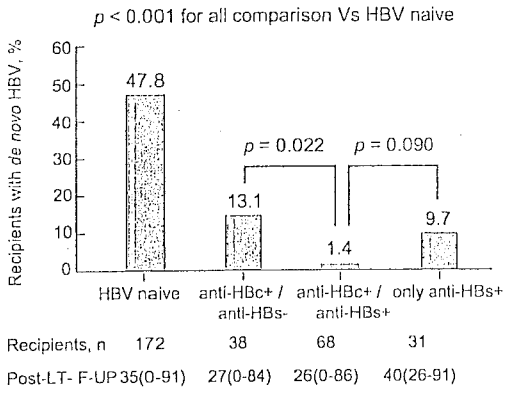

Fig. 1. Risk of *de novo* hepatitis B virus (HBV) infection in HBsAg-negative recipients who received liver grafts from anti-HBc positive donors and no HBV prophylaxis after liver transplantation (LT) in relation to their HBV serological status before transplant.

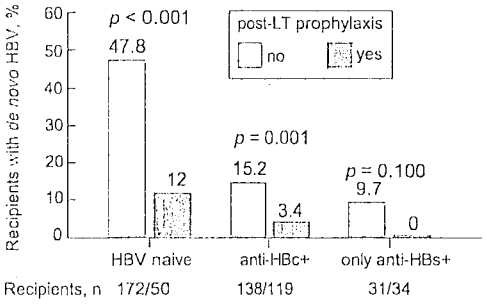

Fig. 2. Risk of *de novo* hepatitis B virus (HBV) infection in HBsAg-negative recipients of liver grafts from anti-HBc positive donors in relation to their pre-transplant HBV serological status and the use of HBV prophylaxis after liver transplantation (LT).

27 months (0.2–84). (b) HBsAg-negative recipients with anti-HBc positivity and anti-HBs positivity. In nine studies [5,10,11,16, 22,25,29,36,37], *de novo* HBV infection was documented in only 1.4% (1/68) of such recipients with anti-HBc positive donors during a median follow-up of 26 (0.2–86) months. The anti-HBs status of the donors was reported in only five studies including just 18 HBsAg-negative recipients positive for anti-HBc with or without positive anti-HBs [5,9,16,36,38], and therefore the impact of the anti-HBs donors' status could not be safely determined.

Anti-HBc positive liver grafts to HBsAg-negative recipients with successful pre-LT vaccination. Seven studies evaluated the development of *de novo* HBV infection in 31 HBsAg-negative recipients who developed anti-HBs after HBV vaccination before LT and received no post-LT prophylaxis [11,16,21,22,24,36,37]. *De novo* HBV infection developed in 3 (9.7%) of them during a median post-LT follow-up of 40 (26–91) months.

Anti-HBc positive liver grafts to HBV naive recipients. During a median follow-up of 35 months (range: 0.1–91), *de novo* HBV infection after LT with grafts from anti-HBc positive donors was detected in 47.8% (89/186) of HBV naive recipients included in 14 studies [5,9–11,16,21,24,27,29,30,37,38,41,42]. Interestingly, the presence of anti-HBs in the donors did not affect the probability of *de novo* HBV infection in HBV naive recipients. In particular, in eight studies [5,9,10,16,21,30,38,41] providing the anti-HBs status in the donor, *de novo* HBV infection developed in 71% (28/39) of recipients with both anti-HBc and anti-HBs positive donors during a follow-up of 37 (0.2–66) months, and in 65% (20/31) of recipients with anti-HBc positive but anti-HBs negative donors during a follow-up of 33 (0.1–91) months ($p = 0.70$) (Fig. 2).

Post-transplant prophylaxis against de novo HBV Infection

Twenty five [5,11,16,19,21–26,28,31–35,40,43–50] studies reported data on post-transplant prophylaxis (HBIG and/or lamivudine and/or HBV vaccination) against *de novo* HBV infection in 366 patients who received liver grafts from anti-HBc positive donors. HBIG alone was used in 96, lamivudine alone in 75, HBIG and lamivudine in 104, HBIG and/or lamivudine in 7, post-LT vaccination with HBIG and/or lamivudine in 81 and post-LT vaccination alone in three cases. *De novo* HBV infection developed in 7.4% (27/363) of recipients who received HBIG and/or lamivudine after LT (combined with post-LT vaccination in 81 cases) and in all 3 cases who received post-LT vaccination alone ($p < 0.001$). In particular, *de novo* HBV infection under HBIG and/or lamivudine was observed significantly more frequently in HBV naive than anti-HBc and/or anti-HBs positive recipients (18/150 or 12% vs 4/153 or 2.6%, $p = 0.006$). *De novo* HBV infection also developed in 8.3% (5/60) of recipients with unknown pre-LT status who received HBIG and/or lamivudine with or without post-LT vaccination (Table 3).

HBIG monoprophylaxis. HBIG (5000 or 10,000 IU intravenously starting during the anhepatic phase) was used as monoprophylaxis for varying intervals after LT in eight studies [11,21,24,33, 35,46,47,50] (Table 3). During a median follow-up of 31 months (range: 3–86), *de novo* HBV infection developed in 18 (18.7%) of 96 recipients: five (27%) had discontinued HBIG and another two (11%) had low serum anti-HBs levels (<50 IU/mL) despite HIBG administration, at the diagnosis of *de novo* HBV infection. In particular, *de novo* HBV infection under HBIG monoprophylaxis developed in 27% (17/63) of HBV naive recipients and 5.8% (1/17) of recipients with past HBV infection ($p = 0.10$) during a median follow-up of 30 (3–86) and 19 (3–86) months, respectively. In addition, *de novo* HBV infection also developed in none of five recipients with successful pre-LT vaccination during a median follow-up of 35 (31–38) months and in none of 11 recipients with unknown pre-LT HBV status who received post-LT prophylaxis with HBIG alone. The impact of recipient's anti-HBs status could not be determined due to limited data.

Lamivudine monoprophylaxis. Since HBIG has several limitations, such as high cost, poor compliance and even low protection particularly in HBV naive recipients [11], lamivudine monoprophylaxis (100–150 mg/day for long periods) against *de novo* HBV infection was also evaluated in six studies [16,19,22,25,26,40] (Table 3). During a median follow-up of 25 (1–69) months, *de novo* HBV infection was observed in 2.6% (2/75) of recipients [1/25 (4.0%) recipients with past HBV infection, 1/33 (3.4%) HBV naive recipients, 0/17 recipients with successful pre-LT vaccination ($p = 0.72$)]. Interestingly, the HBV naive recipient with *de novo* HBV infection developed it after lamivudine discontinuation (Fig. 3).

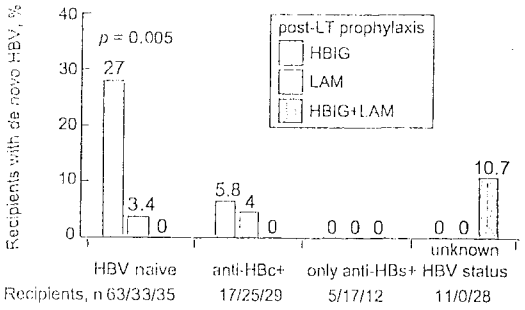

Fig. 3. Risk of *de novo* hepatitis B virus (HBV) infection in HBsAg-negative recipients who received liver grafts from anti-HBc positive donors and HBV prophylaxis after liver transplantation (LT) in relation to their pre-transplant HBV serological status and the type of post-transplant HBV prophylaxis. HBIG, hepatitis B immunoglobulin; LAM, lamivudine.

HBIG and lamivudine combined prophylaxis. Increasing periods of administration of lamivudine as monotherapy is associated with increasing rates of HBV resistance, particularly in patients under immunosuppressive therapy [51]. Thus, the effectiveness of HBIG and lamivudine combination was evaluated in eight studies [22,24,28,31,34,35,40,43] (Table 3). Lamivudine (100–300 mg/day) was given long-term, while HBIG was given short- or long-term at dosages ranging from 400 IU intramuscularly to 10,000 IU intravenously. During a mean follow-up of 39 (range: 1–86) months, *de novo* HBV infection was observed in 2.8% (3/104) of recipients [0/29 recipients with past HBV infection, 0/35 HBV naive recipients, 0/12 recipients with successful pre-LT vaccination, 3/28 (11%) recipients with unknown pre-LT HBV status]. Since the combination of HBIG with lamivudine is the most widely used approach for prevention of post-LT HBV recurrence in patients transplanted for HBV related liver disease, it is often used as prophylaxis against *de novo* HBV infection as well [8]. However, given the low probability of *de novo* HBV infection with lamivudine alone, the benefit of HBIG with lamivudine combined prophylaxis over monoprophylaxis with lamivudine or perhaps a more potent antiviral agent is not clear from the current literature.

HBV vaccination. HBV vaccination after LT has been evaluated as a strategy to prevent *de novo* HBV infection in recipients of grafts from anti-HBc donors in seven studies [5,32,44,45,48–50]. In six studies using post-LT vaccination combined with HBIG and/or lamivudine prophylaxis [5,32,44,45,48,49], *de novo* HBV infection developed in 5.7% (4/81) of recipients during a median post-LT follow-up of 33 months [22–85] (0/19 HBV naive, 2/48 anti-HBc and/or anti-HBs positive and 2/14 with unknown pre-LT HBV status, $p = 0.16$). In contrast, in the only study in which post-LT HBV vaccination was given alone, *de novo* HBV infection was observed in all three (100%) recipients at 14–20 months after transplant [50]. Thus, although data are very limited, monoprophylaxis with HBV vaccination after LT also does not appear to be an effective prophylactic strategy against *de novo* HBV infection in recipients of anti-HBc positive grafts.

Survival of recipients of grafts from anti-HBc positive donors

The 3-year survival of such recipients has been reported to range between 66% and 100%, if they were HBV naive, and between 89% and 100%, if they had past HBV infection [5,9–11,13,16,19,21–26,29–40,43–45,48,49]. The post-transplant survival of recipients of liver grafts from anti-HBc positive and anti-HBc negative donors has been comparatively evaluated in only two studies with contradictory results [9,10]: 4-year survival in recipients with anti-HBc positive donors was significantly lower compared to recipients with anti-HBc negative donors in a US study (56% vs 76%, $p = 0.005$) [9], whereas no significant difference in 4-year survival between these two groups was reported in a similar Spanish study (68% vs 76%, $p > 0.05$) [10].

Outcome of patients with *de novo* HBV infection

Histological characteristics

Histological characteristics were available in 13 studies including 68 patients [9,10,13,21,22,24,30,32,39,41,42,47,52], but liver biopsies at diagnosis of *de novo* HBV infection were performed in only six studies and only 41 patients [10,21,22,24,32,39] (Table 4). Mild inflammation without fibrosis was found in 33, mild to moderate inflammation with portal or bridging fibrosis in 12,

Table 4. Published studies[a] on the course of *de novo* hepatitis B virus (HBV) infection after liver transplantation.

First author, year [Ref.]	Patients with			Course of *de novo* HBV infection	Follow-up,[b] months
	De novo HBV, *n*	Histological findings	HBV therapy		
Prieto (2001) [10]	15	Chronic hepatitis: 12, mild/massive necrosis: 1/2	LAM	Survival: 80% – 3 deaths (recurrent HCV: 1, lymphoma: 1, sepsis: 1)	37
Segovia (2001) [52]	5	Cirrhosis: 1, moderate fibrosis: 1	LAM	Survival: 100%	8
Manzabeita (2002) [11]	4	Mild hepatitis: 1	HBIG ± LAM	LAM resistance: 1 (mild hepatitis)	19–63
Roque-Afonso (2002) [21]	5	Mild inflammation: 4	LAM	LAM resistance after 7–16 months: 5	12
Lee (2004) [50]	3	NA	LAM ± HBIG	Stable course	NA
Jain (2005) [43]	3	NA	ADV (YMDD mutation)	1 death (fulminant liver failure)	NA
Donataccio (2006) [24]	7	Cholestatic hepatitis: 2	LAM	2 deaths (cholestatic HBV: 1, sepsis: 1)	27
Umeda (2006) [47]	9	Mild inflammation/ fibrosis: 5	LAM (in six patients)	Disappearance of HBsAg in 5 patients after 4.6 months under LAM	21

HBIG, hepatitis B immunoglobulin; LAM, lamivudine; NA, not available.

[a] Seven reports of 1–2 cases with *de novo* HBV infection after liver transplantation were not included [22,32,33,36,38,39,44]. In total, 11 recipients (severe hepatitis: 1) received LAM ($n = 10$) or HBIG plus LAM ($n = 1$). All patients had an uneventful course, except for one patient [36] with poor response to LAM treated with addition of adefovir.

[b] After diagnosis of *de novo* HBV infection.

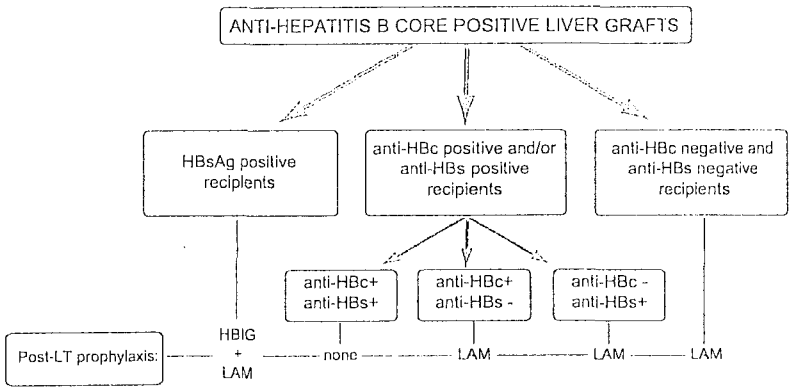

Fig. 4. Proposed algorithm for allocation and management of anti-HBc positive liver grafts. Such grafts should be first offered to HBsAg positive, then to anti-HBc and/or anti-HBs positive and lastly to HBV naive (both anti-HBc and anti-HBs negative) recipients. LT, liver transplantation; HBIG, hepatitis B immunoglobulin; LAM, lamivudine.

severe inflammation and/or cirrhosis in nine, cholestatic hepatitis in three, and non-specific findings in 11 patients.

Course of de novo HBV infection under antiviral therapy

The data on the treatment of *de novo* HBV infection is not well documented, but there are no grounds to expect the efficacy of treatment to be different from that of post-transplant HBV recurrence [51,53]. Only a total of 62 patients are reported. Lamivudine was used in the first 15 studies (combined with HBIG in three) with good initial response [10,11,21,22,24,32,33,36,38,39,43,44,47, 50,52], but lamivudine resistance developed in all five cases after 7–16 months in one study [21] (Table 4). Salvage adefovir therapy was effective in three patients with lamivudine resistance [36,43]. Given the poor resistance profile of long-term lamivudine monotherapy, newer and more potent nucleos(t)ide analogues with low probability of resistance need to be used in this setting despite the lack of data.

Survival of patients with de novo HBV infection

The survival has been reported to range between 66% and 100% during a median follow-up of 48 (3–80) months in 19 studies providing relevant data [5,10,13,16,21,24,30,32,33,35–39,41,42, 47,50,52]. In 14 studies, survival was 100% with a median follow-up of 32 (3–80) months [5,16,21,30,32,33,35–39,47,50,52]. In one study, the outcome of *de novo* HBV infection was significantly better than that of recurrent HBV infection: 3-year survival: 95% vs 60%, ($p = 0.03$) [41]. In the latter study, the causes of death were related to HBV infection in only 2 of 21 non-survivors with *de novo* HBV infection and two additional patients underwent re-LT due to HBV infection.

Conclusions

As the number of patients on LT waiting list continues to grow, the demand for donor organs increases. Thus, the expansion of donor criteria and the inclusion of marginal livers, such as those from anti-HBc positive individuals will be very helpful. In fact, such donors represent a significant source of transplantable organs, particularly in countries with high or intermediate HBV prevalence [54]. The risk of *de novo* post-LT HBV infection is the major limitation of using liver grafts from anti-HBc positive donors, since occult HBV infection in the donor liver may be reactivated in the recipient due to post-LT immunosuppressive therapy. Such liver grafts may be first offered to patients transplanted for HBV related liver disease, as they require life-long anti-HBV prophylaxis in any case (Fig. 4). Although in one study HBsAg-positive recipients of anti-HBc positive liver grafts were suggested to have more frequent and earlier HBV recurrence compared to those of anti-HBc negative liver grafts [20], the risk of HBV recurrence was not reported to be high in several other studies and the donor's anti-HBc status has not been found to affect the post-transplant survival.

Many centres now use grafts from anti-HBc positive donors for HBsAg-negative recipients. Since the probability of such *de novo* HBV infection is substantially lower in anti-HBc and/or anti-HBs positive compared to HBV naive recipients (15% vs 48%), it is reasonable to recommend that liver grafts from anti-HBc positive donors should be preferentially directed to HBV exposed LT candidates (Fig. 4). In the latter, the presence of anti-HBs seems to protect from *de novo* HBV infection and both anti-HBc and anti-HBs positive recipients seem to represent a group that can safely receive anti-HBc positive liver grafts without any post-transplant HBV prophylaxis (probability of *de novo* HBV infection <2%). Pre-LT vaccination alone does not appear to be an effective strategy, as *de novo* HBV infection after LT developed in 10% of successfully vaccinated recipients without any post-LT prophylaxis. However, HBV vaccination should be offered to all naive HBV patients early in the course of non-HBV chronic liver disease (i.e. in the pre-cirrhotic stage), even though additional anti-HBV prophylaxis will be needed in cases of LT with grafts from anti-HBc positive donors. Because of lack of data, no conclusions can be drawn on the effect of the donor's anti-HBs status, which could theoretically reduce the risk of transmission even further.

The use of post-transplant prophylaxis with HBIG and/or lamivudine reduces the overall probability of *de novo* HBV infection in both HBV naive (from 48% to 12%) and anti-HBc and/or anti-HBs positive recipients of anti-HBc positive grafts (from 15% to 3%). According to a recent survey reflecting current clinical practice, prophylaxis with lamivudine and often HBIG is usually used after LT with anti-HBc positive grafts, but it is less likely to be used in anti-HBs positive recipients [8]. Although there are no

good data from single studies on the optimal anti-HBV prophylaxis, several conclusions can be drawn based on all the studies we have reviewed. First, monoprophylaxis with HBIG or HBV vaccination after LT is an ineffective strategy, as it is associated with approximately 20% and 100% risk of *de novo* HBV infection. Monoprophylaxis with lamivudine appears to offer satisfactory protection with <3% risk of *de novo* HBV infection, although it should be noted that the number of reported cases is still small ($n = 75$) and the follow-up relatively short (approximately 2 years). The combination of HBIG and lamivudine is often used empirically in this setting, because of its proven benefit in preventing HBV recurrence after LT for HBV related liver disease [51,55]. However, this combination does not seem to provide a clear benefit compared to lamivudine monoprophylaxis in liver transplant HBsAg-negative patients who receive anti-HBc positive grafts. In fact, the rationale for HBIG use is unclear, as there are no circulating HBsAg coated virions in HBsAg-negative recipients to be neutralised by HBIG. Whether monoprophylaxis with a new nucleos(t)ide analogue with better resistance profile might be a more cost-effective long-term approach in all or in subsets of such transplant patients also remains to be determined. Given the relatively low numbers of cases, the different subgroups of donor–recipient matching with anti-HBc/anti-HBs status and the varied prophylactic interventions, multicentre studies will be required in order to provide evidence-based data.

If *de novo* post-LT HBV infection develops, antiviral treatment is mandatory. Although documentation of transplant details and outcomes is scanty, it is reasonable to think that the efficacy of treatment is similar to that of post-transplant HBV recurrence. Given the poor resistance profile of long-term lamivudine monotherapy and the low potency of adefovir, both entecavir and tenofovir may be the agents of choice today, despite the current lack of relevant data. Entecavir has the advantage of not being nephrotoxic and tenofovir has the advantage of better long-term efficacy in cases of lamivudine resistance.

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REVIEW PAPER

Liver Transplantation Using Hepatitis B Core Antibody – Positive Grafts: Review and University of Tokyo Experience

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Abstract Hepatitis B surface antigen – negative and hepatitis B core antibody – positive grafts were considered unsuitable for transplantation. The number of potential recipients for liver transplantation now exceeds that of potential donor organs, which has led us to reevaluate the feasibility of these grafts. Several strategies involving prophylactic administration of hepatitis B immunoglobulin and/or lamivudine to transplant recipients have been proposed. At the University of Tokyo, we have continued to use hepatitis B immunoglobulin monoprophylaxis with zero recurrence.In this article we report our experience with the use of hepatitis B surface antigen – negative/hepatitis B core antibody – positive grafts with hepatitis B immunoglobulin monotherapy. We conducted a review of the literature regarding the feasibility of these grafts to reconfirm optimal prophylactic strategies for preventing *de novo* hepatitis B virus infection in transplant recipients.

Keywords Hepatitis B virus · *De novo* hepatitis · Living donor liver transplantation · Hepatitis B core antibody · Hepatitis B immunoglobulin

Abbreviations

HBV: Hepatitis B virus
LDLT: Living donor liver transplantation
HBcAb: Hepatitis B core antibody
HBsAb: Hepatitis B surface antibody
HBsAg: Hepatitis B surface antigen
HBIG: Hepatitis B immunoglobulin

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Introduction

Hepatitis B surface antigen (HBsAg) – negative and hepatitis B core antibody (HBcAb) – positive grafts are sources of *de novo* hepatitis B virus (HBV) infections. Therefore, they were considered unsuitable for transplantation during the early 1990s [1–3]. As shown in Table 1, the occurrence of *de novo* HBV hepatitis in recipients that received the grafts might be influenced by the pre-existing HBV immunity of the recipient [4–10].

The number of potential recipients for liver transplantation now exceeds that of potential donor organs, leading us to reevaluate the feasibility of using these grafts. Several strategies involving the prophylactic administration of hepatitis B immunoglobulin (HBIG) and/or lamivudine to the recipients have been proposed [7, 10–20]. Liver transplantation from live donors (LDLT) is currently the most effective alternative to overcome the organ shortage. Live donors are often restricted to the relatives of the recipient. In regions where HBV is prevalent, there is no choice other than a graft from a live donor who is HBsAg-negative/HBcAb-positive.

HBsAg-negative/HBcAb-positive grafts are now important topics in LDLT. The optimal prophylactic strategy remains a matter of debate. We conducted a review of the literature regarding the feasibility of HBsAg-negative/HBcAb-positive grafts to reconfirm optimal prophylactic strategies for preventing *de novo* HBV infection in recipients.

Table 1 Recipient's viral status and *de novo* HBV infection rates after transplant of HBcAb-positive grafts without prophylaxis

Author, year	Recipient viral status (HBsAb/HBcAb)				Total (%)
	+/+	+/−	−/+	−/−	
Douglas, 1992 [1]	ND	ND	ND	ND	3/7 (43)
Chazouilleres, 1994 [2]				7/8	7/8 (88)
Wachs, 1995 [3]				3/6	3/6 (50)
Dickson, 1997 [5]	0/1	1/2	0/1	14/16	18/23 (78)
Dodson, 1997 [6]		0/7	2/15	18/25	20/47 (43)
Uemoto, 1998 [7]		1/1		14/15	15/16 (94)
Prieto, 2001 [8]	0/2	0/2	0/3	15/23	15/30 (50)
Manzarbeitia, 2002 [9]	0/13	1/1	2/11	2/2	3/27 (11)
Donataccio, 2006 [21]		0/1		3/4	3/5 (60)
Barcena, 2006 [40]	0/6		0/3		0/9 (0)

Note. HBsAb, hepatitis B surface antibody; HBcAb, hepatitis B core antibody; ND, not described.

Management protocols for prevention of *de novo* HBV Infection (Table 2)

HBIG monoprophylaxis

Uemoto et al. [7] first reported the successful prevention of *de novo* HBV infection using HBIG in recipients who received HBcAb-positive grafts from live donors. Although some authors followed their prophylaxis, the risk of reactivation remained high [4, 9, 11, 15, 21]. Decreased hepatitis B surface antibody (HBsAb) titer seems to be a significant risk factor for *de novo* infection [15]. More recent reports with satisfactory results targeted higher HBsAb levels for an indefinite period [19].

Lamivudine and HBIG

Dodson et al. [11] reported therapy using a combination of prophylactics: HBIG doses ranged from 10,000 IU only during the anhepatic phase [13] to 10,000 IU for seven days after transplantation [11, 14]. The minimum amount of HBIG required to prevent *de novo* infection is unclear. In either case, lamivudine was started after the initial HBIG administration or simultaneously. Suehiro et al. [22] reported that HBIG

Table 2 Prophylaxis for HBcAb-positive graft and infection rate

Author, year	*N*	Followup (months)	Protocols	Rate (%)
HBIG monotherapy				
Radomski, 1996 [4]	1	8	2000 IU/month	1/1 (100%)
Uemoto, 1998 [7]	3	13–24	100 IU/kg for 7 days and 1000 IU/m thereafter	0/3 (0%)
Dodson, 1999 [11]	1	11	10,000 IU for 7 days and monthly for 6 months, 1000 IU biweekly for 18 month	1/1 (100%)
Roque-Afonso, 2002 [15]	12	6–36	5000 IU for 7 days and subsequently to keep HbsAb > 100 IU/L	1/12 (8%)
Lee, 2004 [19]	18	13–80	10,000 IU for 7 days and subsequently to keep HbsAb > 200 IU/L	0/18 (0%)
Donataccio, 2006 [21]	6	18–62	10,000 IU for 7–10 days and stopped	4/6 (67%)
Donataccio, 2006 [21]	4	11–34	10,000 IU for 7–10 days and subsequently continued indefinitely	0/4 (0%)
Takemura, 2006	17	3–96	10,000 IU in anhepatic phase and subsequently to keep HbsAb > 200 IU/L for a year, then > 100 IU/L indefinitely	0/17 (0%)
HBIG + Lam				
Dodson, 1999 [11]	15	6–25	HBIG; 10,000 IU for 7 days and monthly for 6 months, 1000 IU biweekly for 18 months. LAM; 150 mg/day	0/15 (0%)
Holt, 2002 [14]	12	2–38	HBIG; 10,000 IU for 7 days, LAM; 300 mg/day	0/12 (0%)
Jain, 2005 [20]	28	36 ± 19[a]	HBIG; 10,000 IU for 4 days, LAM; 100 mg/day	3/28 (11%)
Suehiro, 2005 [22]	22	25–86	HBIG; 10,000 IU in anhepatic phase, 2000 IU for 7 days and subsequently to keep HbsAb > 100 IU/L, LAM; 100 mg/day	0/22 (0%)
Lam				
Yu, 2001 [12]	9	2–36	LAM; 100 or 150 mg/day	0/9 (0%)
Prakoso, 2006 [24]	10	2–69	LAM; 100 mg/day	0/10 (0%)

Note. HBIG, hepatitis B immunoglobulin; LAM, lamivudine.

[a] Mean ± standard error.

Table 3 Tailored approach based on graft HBVDNA and recipient HBV immunity

Author, Year	*N*	HBVDNA in donor		Recipient HBsAb	Protocols
		Graft	Serum		
Loss, 2001 [13][a]	1	–	–	ND	10,000 IU of HBIG in anhepatic phase + LAM 150 mg/day → discontinued after confirming the HBVDNA status (graft and donor serum)
	0	+	+	ND	HBIG + LAM → continued
	5	+	NA	ND	HBIG + LAM → LAM; 150 mg/day
Fabrega, 2003 [16][a]	7	–	–	ND	10,000 IU of HBIG for 7 days + Lam; 100 mg/day → discontinued after confirming the HBVDNA status (graft and donor serum)
	0	+	+	ND	HBIG + LAM → LAM; 100 mg/day
Nery, 2003 [17][a]	10	+	+	ND	10,000 IU HBIG for 7 days, weekly for 1 month, and monthly for 6 months + LAM; 100 mg/day
	13	–	–	–	LAM; 100 mg/day
	13	–	–	+	None
	2	NA	ND	–	LAM; 100 mg/day
	5	NA	ND	+	None

Note. HBVDNA, hepatitis B virus deoxyribonucleic acid; HBIG, hepatitis B immunoglobulin; NA, not available; ND, not described; LAM, lamivudine.

[a]No reinfection was seen in all the patients with these protocols.

use with lamivudine over an indefinite period of time might have prevented *de novo* infection in 22 patients receiving HBsAg-negative/HBcAb-positive grafts.

Long-term use of lamivudine is associated with the risk of mutated HBV infection. Jain et al. [20] reported 3 of 28 patients with *de novo* mutated HBV infection who used a protocol of short-term treatment with HBIG (10,000 IU HBIG for 4 days) and indefinite use of lamivudine (100 mg/day). Among these three infected patients, two had a YMDD mutation. Yen et al. [23] experienced a case complicated with a lamivudine-resistant mutation while using a similar protocol.

Lamivudine monoprophylaxis

Yu et al. [12] advocated lamivudine monoprophylaxis. HBV infection was prevented in nine patients who received HBsAg-negative/HBcAb-positive allografts. Six of the nine patients died of recurrent hepatocellular carcinoma (HCC) and sepsis, however, and the followup periods were limited (3–36 months). Prakoso et al. [24] reported that they successfully prevented HBV infection in ten HBsAg-negative patients with lamivudine monotherapy.

Tailored approach (Table 3)

Loss et al. [13] and Nery et al. [25] advocated that prophylaxis should be selected according to the serum and liver HBVDNA status of the donor or the recipient's preoperative serology. Loss et al. administered HBIG during the anhepatic phase and started lamivudine on postoperative day 1. If HBVDNA was detected in neither the donor liver nor serum, lamivudine was stopped. If HBVDNA was detected in the donor liver and serum, HBIG was continued with lamivudine. Fabrega et al. [16] started prophylaxis with a combination of HBIG and lamivudine on the first operative day until they obtained HBVDNA results from the donor samples. They stopped the prophylaxis when the donor's HBVDNA in serum and liver tissue was negative, even in a naïve recipient. None of their seven patients developed *de novo* hepatitis B with a mean followup period of 23 months.

The protocol of Nery et al. [17] was more complicated because the strategy was changed by not only the results of the donor HBV profile but also the recipient's HBV serology. The recipients of HBVDNA-positive grafts received HBIG and lamivudine combination therapy. If the donor serum and liver graft HBVDNA were both negative and the recipient was HbsAb-negative, lamivudine monotherapy was selected. If the recipient was HbsAb-positive, no therapy was administered. Their selective protocol successfully prevented 43 patients from reactivation of HBV, including 18 patients without prophylaxis. Two patients were excluded from their study because of low compliance; both recipients developed *de novo* hepatitis. Their allografts were HBVDNA-negative but they were infected with hepatitis. One was naïve and the other was only HBcAb-positive preoperatively.

A tailored approach is based on the results of testing for HBVDNA in the allografts. The sensitivity for HBVDNA detection, however, depends on the methodology [26]. Van Thiel et al. [27] reported that HBVDNA was detected in 11 (8%) of 133 livers from HBsAg-negative/HBcAb-positive donors. Marusawa et al. [28] reported that HBVDNA was detected in 14 of 17 grafts (82%) from HBcAb-positive donors.

Suehiro et al. [22] detected HBVDNA in 20 of 20 grafts. HBVDNA in all grafts was detected by polymerase chain reaction (PCR) methods, but the details of the methods differed. Van Thiel used primers targeting surface antigen sequences with a sensitivity of an approximately 600 HBV copies per milliliter serum sample. Marusawa used primers targeting the surface and pre-C/C region. The first PCR products were subjected to either Southern blotting analysis or to a second PCR amplification (seminested PCR for pre-C/C region and nested PCR for the surface region). The sensitivity of their assay was 10 copies per 20 μg DNA. Suehiro selected real-time PCR with a sensitivity of 10 copies per gram DNA.

Vaccination

The response rates to recombinant hepatitis B vaccine in liver transplantation candidates (with HBV unrelated liver failure) varied from 16% to 62% [29–38]. It is difficult to explain the variations in hepatitis B vaccine response rates. HBsAb titers rapidly decline and become undetectable in a significant proportion of patients after transplantation. HBsAb titers become undetectable in 37%–73% of the responders within one year after transplantation [33, 35, 38]. Dominguez et al. [30] reported a 62% response rate with 40-μg hepatitis B vaccinations three times preoperatively with a one-month interval and an additional three doses for nonresponders. Conventionally, patients with HBsAb titers of more than 10 IU/L are considered immunized [39].

Kaohsiung's group performed preoperative vaccination in all patients awaiting transplantation because approximately 80% of adults are HBcAb-positive in Taiwan [10]. They reported *de novo* HBV infection in three of eight preoperatively immunized patients who received an HBcAb-positive graft. They made a policy change [18] and began to use lamivudine after surgery with preoperative vaccination. Thereafter, none of 44 patients developed *de novo* hepatitis. Barcena et al. [40] vaccinated only those who were HBsAb- or HBcAb-negative and receiving an HBcAb-positive allograft. No postoperative prophylaxis against HBV was performed in their protocol. They immunized 14 recipients with 40-μg hepatitis B vaccinations three times with a 15-day interval, although the vaccine response rate was not described. One of the 14 recipients developed *de novo* HBV infection after receiving an HBcAb-positive liver; this might have occurred because of an immune escaped HBV mutant with a structural variation in the epitope of the surface antigen recognized by the HBsAb [41, 42].

University of Tokyo experience

From January 1996 to December 2005, 351 LDLT were performed at the University of Tokyo. All donors were HBsAg-negative and 34 (10%) were HBcAb-positive. Of the recipients of HBsAg-negative/HBcAb-positive grafts, 19 were HBV-unrelated recipients and the others had HBV-related cirrhosis. The 19 liver grafts were the subjects of the study. The serum HBV status included HbcAb- and HBsAb-negative ($n = 9$), HbcAb- and HBsAb-positive ($n = 5$), HBcAb-positive ($n = 2$), or HBsAb-positive ($n = 3$). There were 14 men and 5 women with a median age of 51 years [21–64]. The immunosuppression regimen for all recipients consisted of tacrolimus and corticosteroids.

Postoperative prophylaxis consisted of HBIG monotherapy. A total of 10,000 IU HBIG was administrated intravenously during the anhepatic phase. HBIG was administered once a month to maintain the HBsAb level above 200 IU/L during the first year and above 100 IU/L thereafter. We do not use nucleotide analogs for prophylactics to those who received HBcAb-positive graft to avoid the emergence of multidrug resistance.

Our strategy of anhepatic and low-dose HBIG monoprophylaxis prevented perioperative *de novo* HBV infection in all 19 patients that were preoperatively HBsAg-negative and received HBcAb-positive livers. Among the 19 patients, 3 patients died of HBV-unrelated causes between 2 and 13 months after transplantation without any evidence of HBV infection. Two patients were dropped from the prophylaxis protocol because of poor compliance. They skipped the monthly HBIG administration and as a result developed *de novo* HBV infection. Preoperatively, one was naïve and the other was HBsAb- and HBcAb-positive. HBsAb titers at the onset decreased to 10 and 15 IU/L. *De novo* hepatitis was defined as the development of positive serum HBsAg. Their HBsAg were detected 51 and 35 months after the operation. Hepatitis B e antigen became positive and serum HBVDNA was detected. They received antiviral therapy using lamivudine and their hepatitis B e antigen and HBVDNA became negative thereafter. The remaining 14 patients showed no evidence of HBV infection with followup periods of 3–86 months (median = 31 months).

The median amount of HBIG that was used during the first month of transplantation was 12,000 IU (10,000–18,000 IU) and that during the following 11 months was 14,000 IU (12,000–31,000 IU). After the first postoperative year, 10,000 IU HBIG (8000–22,000 IU) was required each year to keep HBsAb levels over 100 IU/L.

Future possible alternatives

Lamivudine is often used to treat a patient with chronic hepatitis B but antiviral drug-resistant mutation frequently develops. Resistance to adefovir dipivoxil is less common than for lamivudine [43]. Adefovir dipivoxil shows favorable outcome in patients with *de novo* hepatitis B after liver

transplantation [44] and in the patients with lamivudine-resistant hepatitis B [45, 46]. Recently, alternative nucleoside analogs adefovir dipivoxil, entecavir [47], telbivudine [48], and tenofovir [49] were administered efficiently in treating wild-type and/or mutated HBV. All of them also have the potential to be used for prophylaxis against *de novo* HBV infection from HBcAb-positive allograft. However, some reports revealed the emergence of mutated HBV which showed resistance not only to lamivudine but also to adefovir dipivoxil [43], entecavir [50], and telbivudine [48].

Conclusions

De novo HBV infection can be prevented with HBcAb-positive grafts when an adequate strategy is applied. HBIG monotherapy can prevent HBV infection from HBcAb-positive liver grafts. Lamivudine use can be reserved for *de novo* HBV infection. Lamivudine or preoperative vaccination monotherapy are still controversial therapies. Vaccination with lamivudine prophylaxis, however, is promising. A tailored approach might reduce the unnecessary administration of antiviral prophylaxis to a recipient. Further studies are needed to elucidate the optimal prophylactic treatment.

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参考資料３

肝臓移植希望者（レシピエント）選択基準

１．適合条件

（１）ＡＢＯ式血液型

ＡＢＯ式血液型の一致（identical）及び適合（compatible）の待機者を候補者とする。

（２）前感作抗体

当面、選択基準にしないが、必ず検査し、登録する。

（３）ＨＬＡ型

当面、選択基準にしないが、必ず検査し、登録する。

（４）搬送時間（虚血許容時間）

臓器提供者（ドナー）の肝臓を摘出してから１２時間以内に血流再開することが望ましい。

２．優先順位

（１）医学的緊急性

予測余命が１ヶ月以内	９点
予測余命が１ヶ月～６ヶ月以内	６点
予測余命が６ヶ月～１年以内	３点
予測余命が１年を超えるもの	１点

ただし、先天性肝・胆道疾患及び先天性代謝異常症については、肝臓移植が治療的意義を持つ時期、患者の日常生活に障害が発生している状態及び成長障害がある状態を考慮の上、上表に規定する点数のいずれかを用いることがある。

（２）ＡＢＯ式血液型

ＡＢＯ式血液型が一致	１．５点
ＡＢＯ式血液型が適合	１．０点

３．具体的選択方法

適合条件に合致する移植希望者（レシピエント）が複数存在する場合には、優先順位は、以下の順に勘案して決定する。

（1）臓器の移植に関する法律第６条の２の規定に基づき、親族に対し臓器を優先的に提供する意思が表示されていた場合には、当該親族を優先する。

ただし、ＨＬＡの適合度を必ず確認し、臓器提供者（ドナー）のＨＬＡ－Ａ、ＨＬＡ－Ｂ、ＨＬＡ－ＤＲのすべてにホモ接合体が存在し、移植希望者（レシピエント）が臓器提供者（ドナー）のハプロタイプを共有するヘテロ接合体である場合には、移植片対宿主病（ＧＶＨＤ）の危険性が高いため、除く。

（2）２．の（1）、（2）の合計点数が高い順とする。ただし、これらの条件が同一の移植希望者（レシピエント）が複数存在した場合は、待機期間の長い者を優先する。

（3）（1）又は（2）で選ばれた移植希望者（レシピエント）が肝腎同時移植の待機者である場合であって、かつ、臓器提供者（ドナー）から肝臓及び腎臓の提供があったときには、当該待機者に優先的に肝臓及び腎臓を同時に配分する。また、選ばれた移植希望者（レシピエント）が肝腎同時移植の待機者の場合であって、かつ、臓器提供者（ドナー）から肝臓、膵臓及び腎臓の提供があったときには、膵臓移植希望者（レシピエント）選択基準で選ばれた移植希望者（レシピエント）が膵腎同時移植の待機者である場合であっても、当該肝腎同時移植の待機者に優先的に肝臓及び腎臓を同時に配分する。

なお、選ばれた肝腎同時移植の待機者が優先すべき親族でない場合であって、腎臓移植希望者（レシピエント）が優先すべき親族であるときや膵腎同時移植希望者（レシピエント）が優先すべき親族であるときは、当該腎臓移植希望者（レシピエント）や膵腎同時移植希望者（レシピエント）が優先される。

（4）（3）により、肝腎同時移植希望者（レシピエント）が選定されたものの、肝臓が移植に適さないことが判明した場合には、腎臓移植希望者（レシピエント）選択基準で選ばれた腎臓移植希望者（レシピエント）に腎臓を配分する。

４．その他

ＡＢＯ式血液型の取扱いや優先順位の点数付け等、当基準全般については、今後の移植医療の定着及び移植実績の評価を踏まえ、適宜見直すこととする。

また、将来ネットワークが整備され、組織的にも機能的にも十分機能した場合は、改めてブロックを考慮した優先順位を検討することが必要である。

参考資料４

肝臓移植希望待機患者及び小腸移植希望待機患者の状況

＜肝臓＞

2010.9.30現在

移植希望者数　254 名

【血液型】

A	102
B	59
O	73
AB	20
計	254

【性別】

男	148
女	106
計	254

【年代】

0-9歳	5
10-19歳	4
20-29歳	18
30-39歳	39
40-49歳	54
50-59歳	84
60-69歳	47
70歳-	3
計	254

15歳未満	5

【原疾患】

劇症肝炎	0
先天性肝・胆道疾患	16
先天性代謝異常症	8
Budd-Chiari症候群	8
原発性胆汁性肝硬変	21
二次性胆汁性肝硬変	2
原発性硬化性胆管炎	39
C型ウイルス性肝硬変	56
B型ウイルス性肝硬変	41
アルコール性肝硬変	9
その他	54
計	254

【医学的緊急度】

予測余命が1ヶ月以内	0
予測余命が1ヶ月～6ヶ月	104
予測余命が6ヶ月～1年	123
予測余命が1年以上	27
計	254

【待機期間】

1年未満	80
1年以上2年未満	73
2年以上3年未満	44
3年以上4年未満	22
4年以上5年未満	8
5年以上	27
計	254

2010/10/15

＜小腸＞

移植希望者数　4 名

【血液型】

A	2
B	1
O	1
AB	0
計	4

【性別】

男	2
女	2
計	4

【年代】

0-9歳	1
10-19歳	1
20-29歳	1
30-39歳	1
40-49歳	0
50-59歳	0
60-69歳	0
70歳-	0
計	4

15歳未満	1

【原疾患】

腹壁破裂	0
腸軸捻	0
壊死性腸炎	0
腸閉鎖	0
上腸間膜動脈血栓症	0
外傷	0
クローン病	0
その他	4
計	4

原疾患その他の内訳	
短腸症候群	1
短腸症候群、生体小腸移植後、慢性拒絶反応	1
ヒルシュスプルング病類縁疾患	1
慢性偽性腸閉塞(CIIP)	1

【医学的緊急度】

Status1	1
Status2	0
Status3	3
計	4

【待機期間】

1年未満	4	(59～338日)
1年以上2年未満	0	
2年以上3年未満	0	
3年以上4年未満	0	
4年以上5年未満	0	
5年以上	0	
計	4	

2010/10/15

参考資料５

脳死肝移植　適応要件の変更希望

希望内容要約：

乳児劇症肝不全が待機リストにいる場合、現行の血液型一致による加点(+1.5点)を一律に加えて、乳児劇症肝不全には、血液型適合不適合にかかわらず優先的に移植肝が分配されるようにすること。

根拠説明：

１．乳児劇症肝不全症例の頻度とその移植成績

日本小児肝臓病研究会がＷＧを作って調査を行った結果が 2007 年に公表されているが（参考論文１）、1995 年から 2005 年の 10 年間に、国内小児劇症肝不全は 105 例が集計され、その３５％にあたる、37 例が乳児症例であった。成因として最も多いのは原因不明の 20 例となっている（表１）。年代別では、１歳前の乳児が最も多かった(図 1)。年代別の移植成績がこの集計では不明であるが、表２にあるごとく、46 例の原因不明劇症肝不全症例中、37 例が移植を受け、67%が救命されており、非移植９例の救命率 11%と比して有意に高い救命率であった。

日本肝移植研究会の全国集計でも、年間約 30 例の小児劇症肝不全が移植を受けているが、上記乳児の割合から考えると、移植を受ける乳児症例は概ね 10 例と考えられる。

（参考論文１：乾あやの、位田　忍、他。急性肝不全における内科的治療と肝移植の進歩。本邦における小児期の劇症肝不全。　日本腹部救急医学会雑誌　29（４）563-589、2009}

２．血液型不適合移植の年齢による成績の差

劇症肝不全症例が少なく、統計的解析が難しいが、比較的多い京都大学の症例データを用いた解析では、乳児劇症肝不全の術後生存率は、むしろ不適合症例の方が良い傾向にあった（図 2)。1-2 歳症例は不適合症例が無く、比較が出来なかった（図 3)。２歳以上、18 歳未満症例でも、不適合移植の方が良い傾向にあったが、それ以上の成人では、不適合の方が悪かった（図 4、5)。

さらに、日本肝移植研究会の 2008 年末までの全国生体肝移植集計では、18

歳未満小児 1939 例中、12.5%の 243 例が不適合症例であった(表 3)。全年齢での統計比較では、不適合が有意に不良であるが（図 6)、年齢層で分けると、2 歳未満症例は、それ以上の症例より有意に良い成績で、全体の適合症例に匹敵するものであった(図 7)。
米国の脳死肝移植症例における検討でも、乳児、小児年齢層での血液型不適合肝移植成績は、適合例のそれと同等の成績であることが示されている（参考論文２)。

３．上記を踏まえて適応要件変更を希望する理由
一般に血液型不適合肝移植は一致や適合肝移植に比べると成績が不良であるとされ、また、血液型の人口内比率も考慮して、現行では、脳死肝移植での肝臓提供優先順位には、医学的緊急性の点数に、血液型一致+1.5、適合+1.0 の加点がなされて優先度が決定されている。これによれば、例えば、劇症肝不全の乳児が待機中（緊急度 9 点)、血液型一致の緊急度 6 点レシピエントがいても、９+0＞6+1.5、で乳児に肝臓が提供されることとなるが、同じ 9 点に血液型適合レシピエントがいた場合には、たとえ、待機期間が長くても、当該乳児には肝臓が提供されないこととなる。乳児血液型不適合肝移植の成績が、適合移植と不変であるとの上記証左から、時宜を得た移植を受けることが出来ない場合の致命的結果を考慮し、少なくとも 1 歳未満の乳児に限って、血液型適合度による点差を無視して緊急度のみに沿った肝臓提供システム構築を望む。該当する乳児肝移植の予想症例数は多くても年間 10 例以下と目され、また、もしこの年齢層が優先度第一位となれば、積極的なドナー肝の分割によって、同緊急度での成人症例にも大きな不利益を与えないものと考える。

添付資料１　　文献報告（米国での集計）

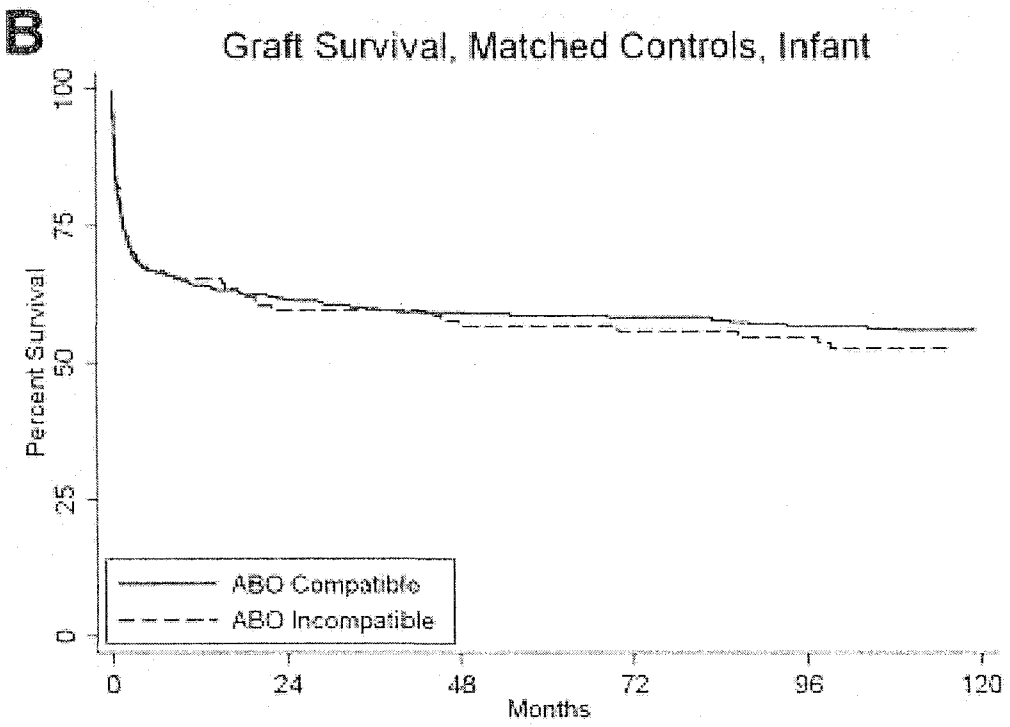
ABO-Incompatible Deceased Donor Liver Transplantation in the United States: A National Registry Analysis

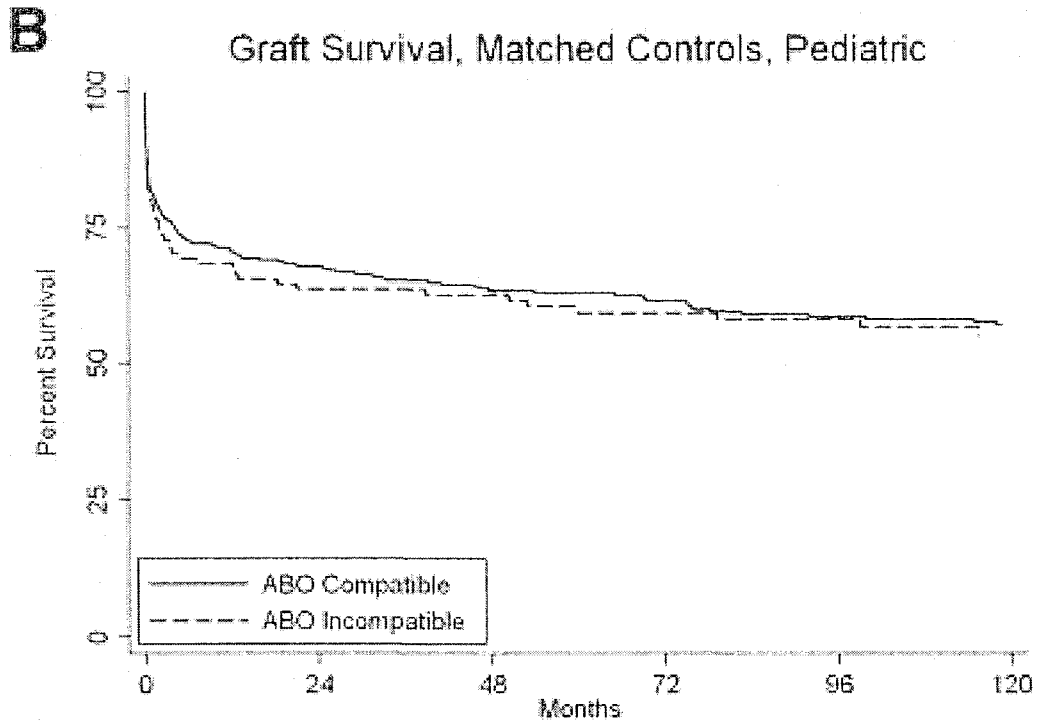
Zoe A. Stewart, et al.

Department of Surgery, The Johns Hopkins University School of Medicine, Baltimore, MD

Liver Transpl 15:883-893, 2009.

要約：米国のＵＮＯＳ（全米臓器分配機構）統計から、2000年以降に行われた、１歳前乳児（156例）、2-17歳小児（170例）、それ以上の成人(667例)の、血液型不適合脳死肝移植について、その成績を評価した。
ドナー、レシピエントの年齢や術前状態などを同等にそろえた血液型適合対照群に比べて、成人症例では血液型不適合肝移植における術後生着率は有意に悪かったのに比べ、乳児や小児では同等の成績が得られた。この傾向は、米国での臓器配分システムにも影響を与える可能性がある。


B
Graft Survival, Matched Controls, Infant
Percent Survival
0
25
50
75
100
ABO Compatible
ABO Incompatible
0
24
48
72
96
120
Months


B
Graft Survival, Matched Controls, Pediatric
Percent Survival
0
25
50
75
100
ABO Compatible
ABO Incompatible
0
24
48
72
96
120
Months

B

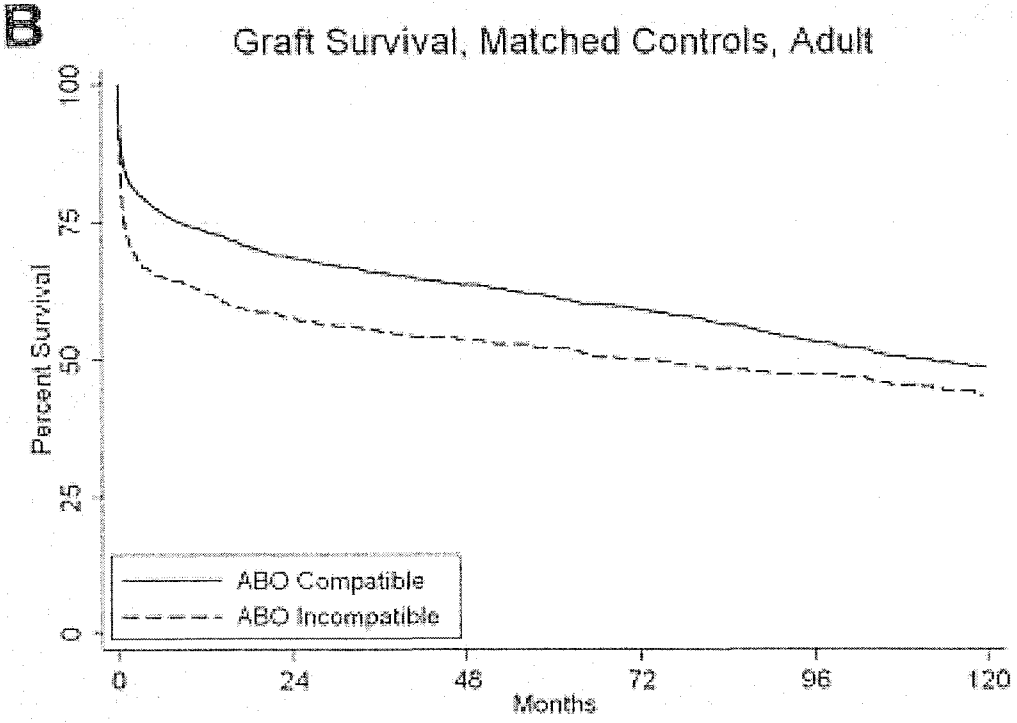

Graft Survival, Matched Controls, Adult
Percent Survival
0
25
50
75
100
ABO Compatible
ABO Incompatible
0
24
48
72
96
120
Months

表1

	劇症 肝不全	急性肝炎 重症型	合計 ('95-'05)	米国小児* ('99-'04)
	105	30	135	348
	58:47	20:10	78:57	157:143
	5歳(35%)	7歳(33%)	(35%)	(24%)
	28(26%)	6(20%)	34(25%)	[illegible]
	9 (9%)	2(6%)	11(8%)	[illegible]**
	20(19%)	10(33%)	30(22%)	[illegible]
	2 (2%)	1(3%)	3(2%)	22(6%)
	46 (44%)	11(38%)	57(43%)	[illegible]

**45/65はアセトアミノフェンによる

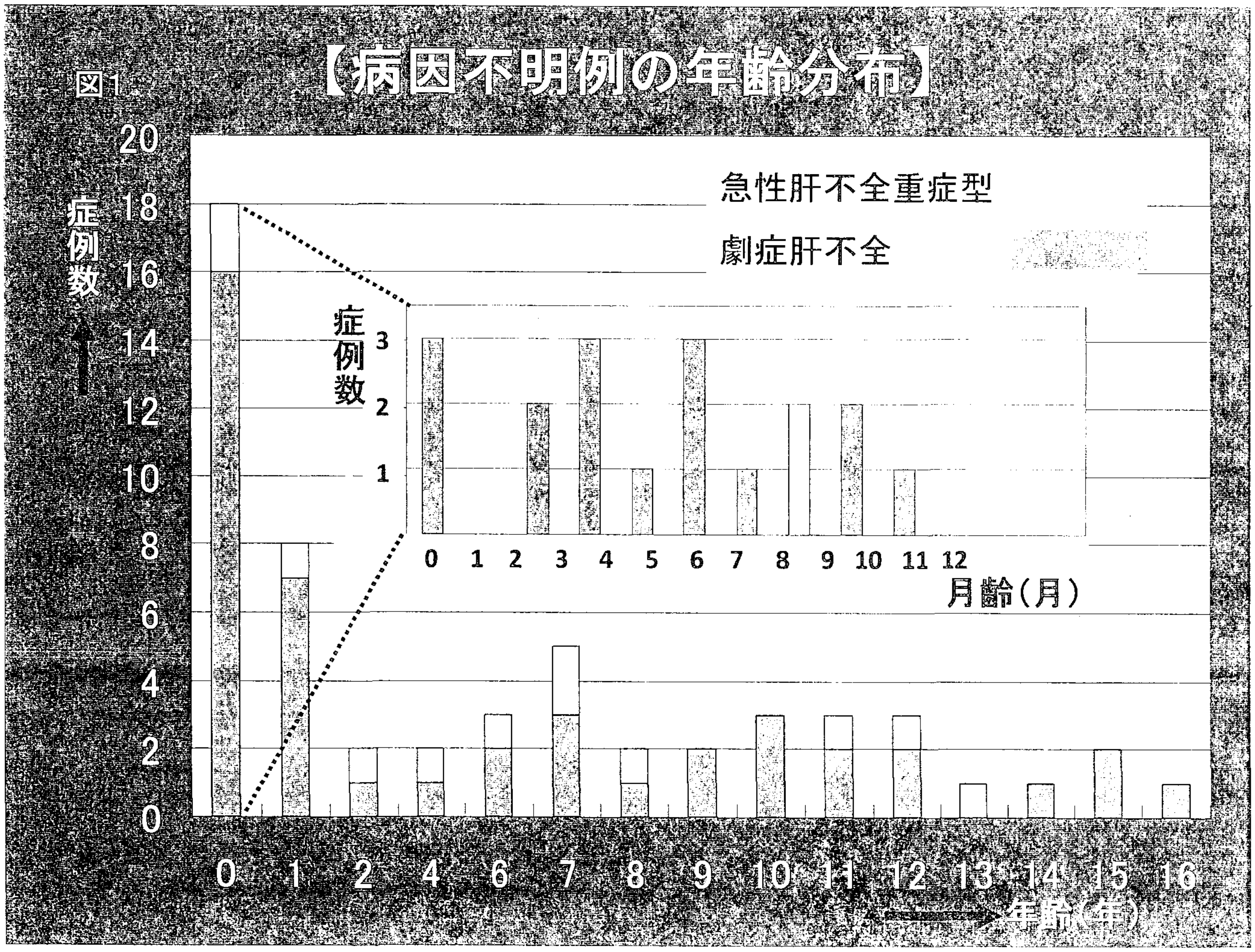


表2

【病因不明例の予後】

PT<40%　57例 (100%)　Coma≧ grade Ⅱ　46例 (79%)
(劇症肝不全例)

	劇症肝不全		急性肝不全重症型
症例数	46例		11例
全症例の救命率	58%		91%
1歳未満例数（救命率）	15（47%）		2（100%）
1歳以上例数（救命率）	31（65%）		9（89%）
移植例数　（救命率）	37（67%）	P<0.001	0
非移植例数（救命率）	9（11%）		11（91%）

図2　（京都大学症例）

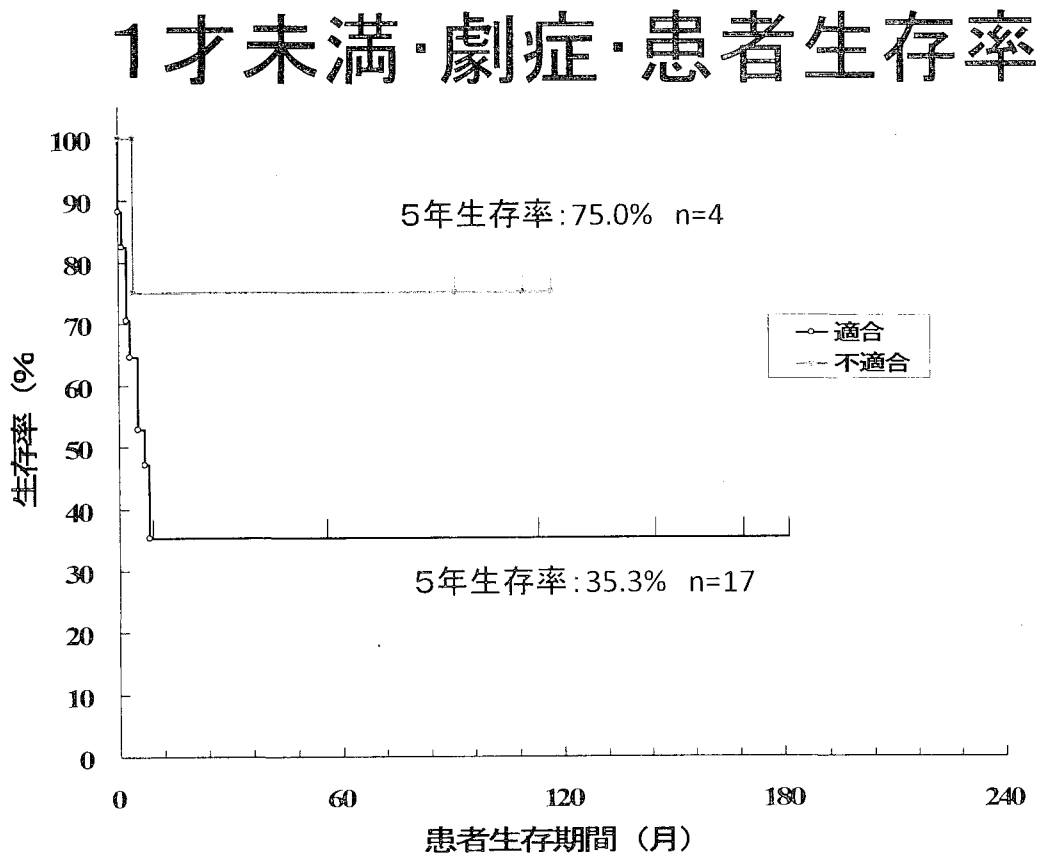


図3　（京都大学症例）

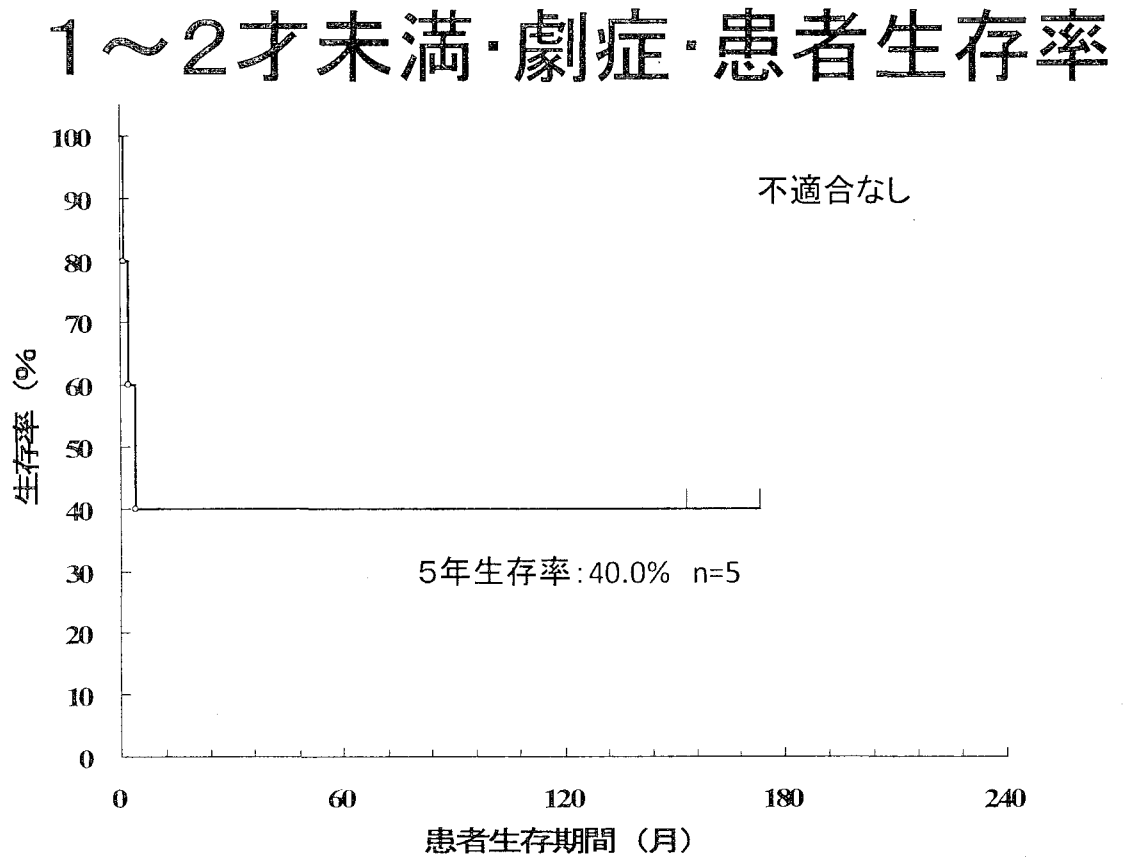


図4　（京都大学症例）

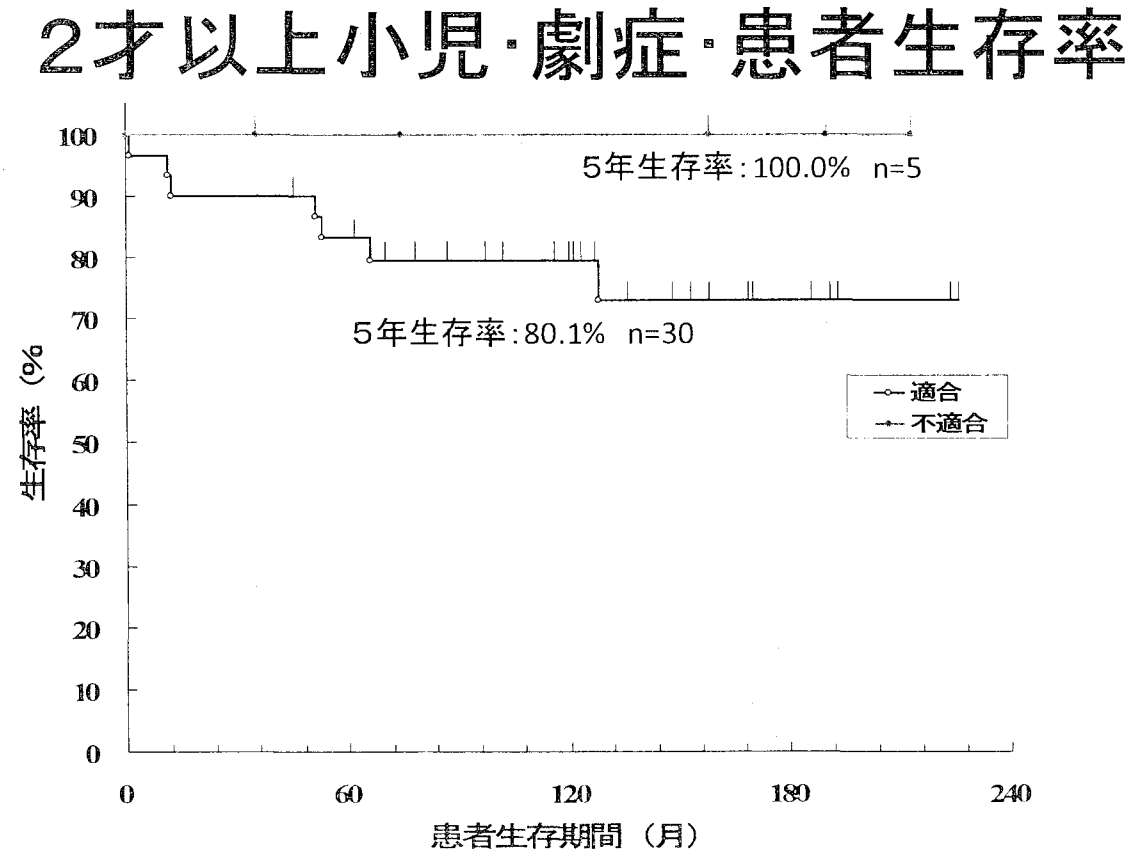


図5　　（京都大学症例）

18才以上・劇症・患者生存率

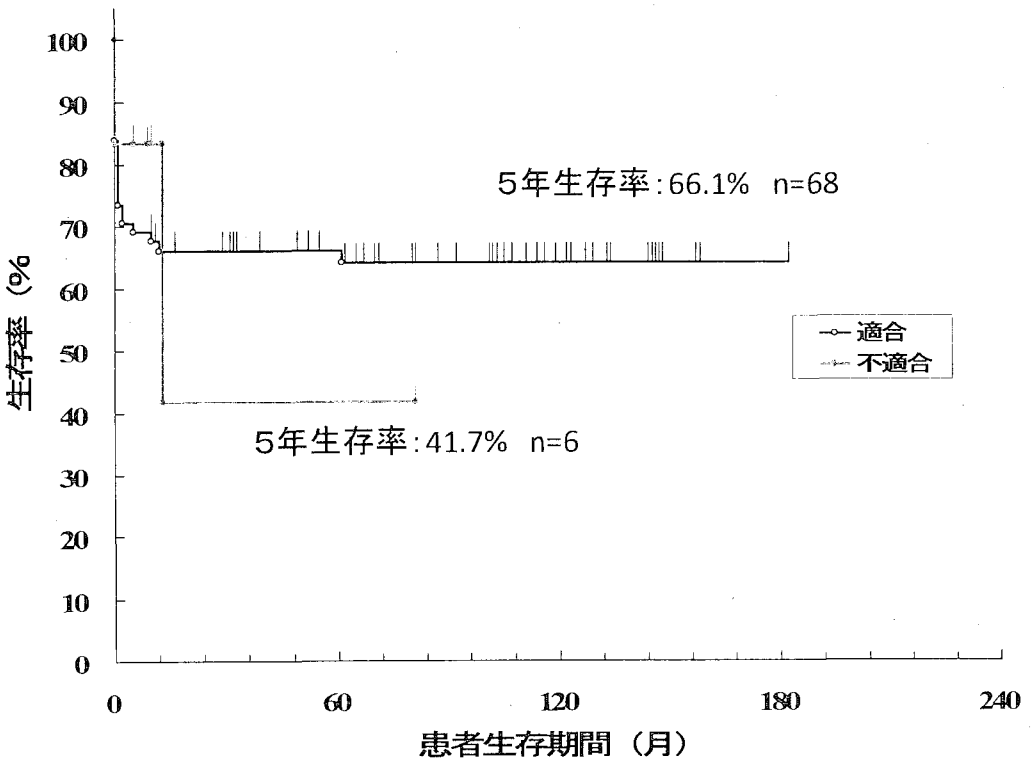


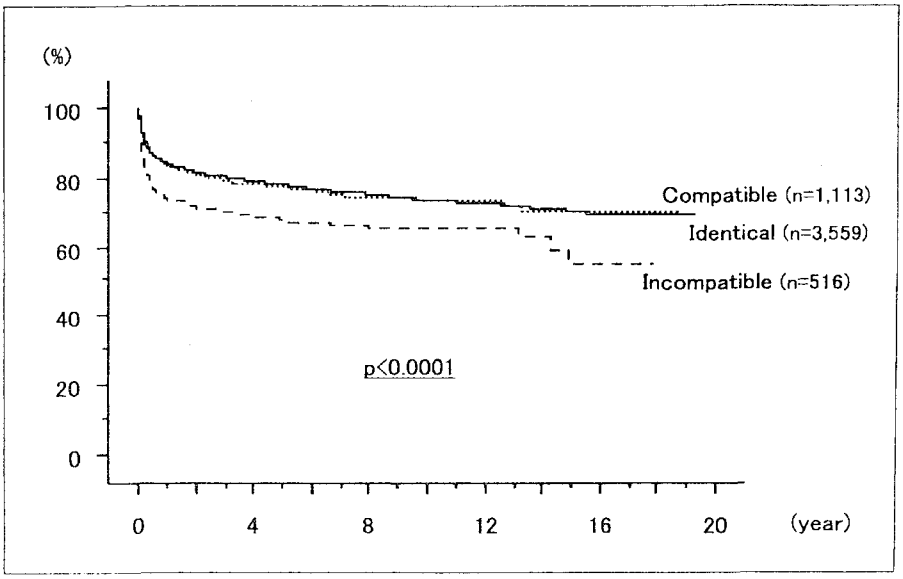
表3

生体肝移植におけるレシピエントとドナーのABO血液型適応度

	Age of The Recipient		Total
	＜ 18 y.o.	≧ 18 y.o.	
Identical	1,305	2,254	3,559
Compatible	391	722	1,113
Incompatible	243	273	516
	1,939	3,249	5,188

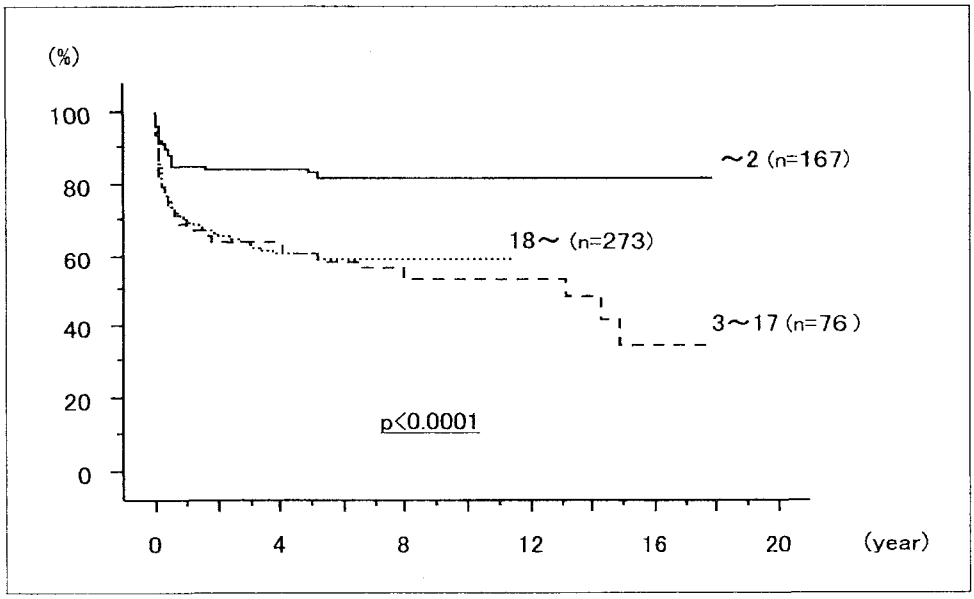
Japanese Liver Transplantation Society

図6



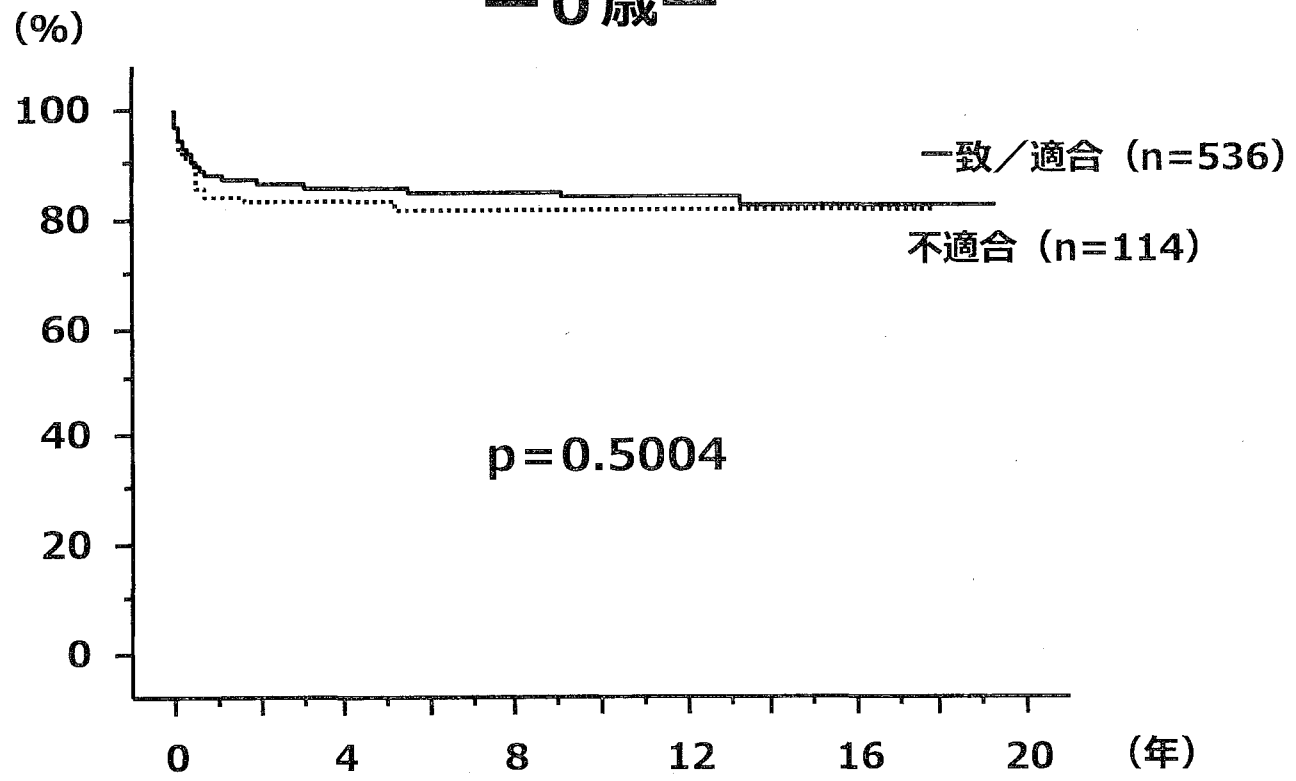
生体肝移植における ABO 血液型適合度別の累積生存率

図7

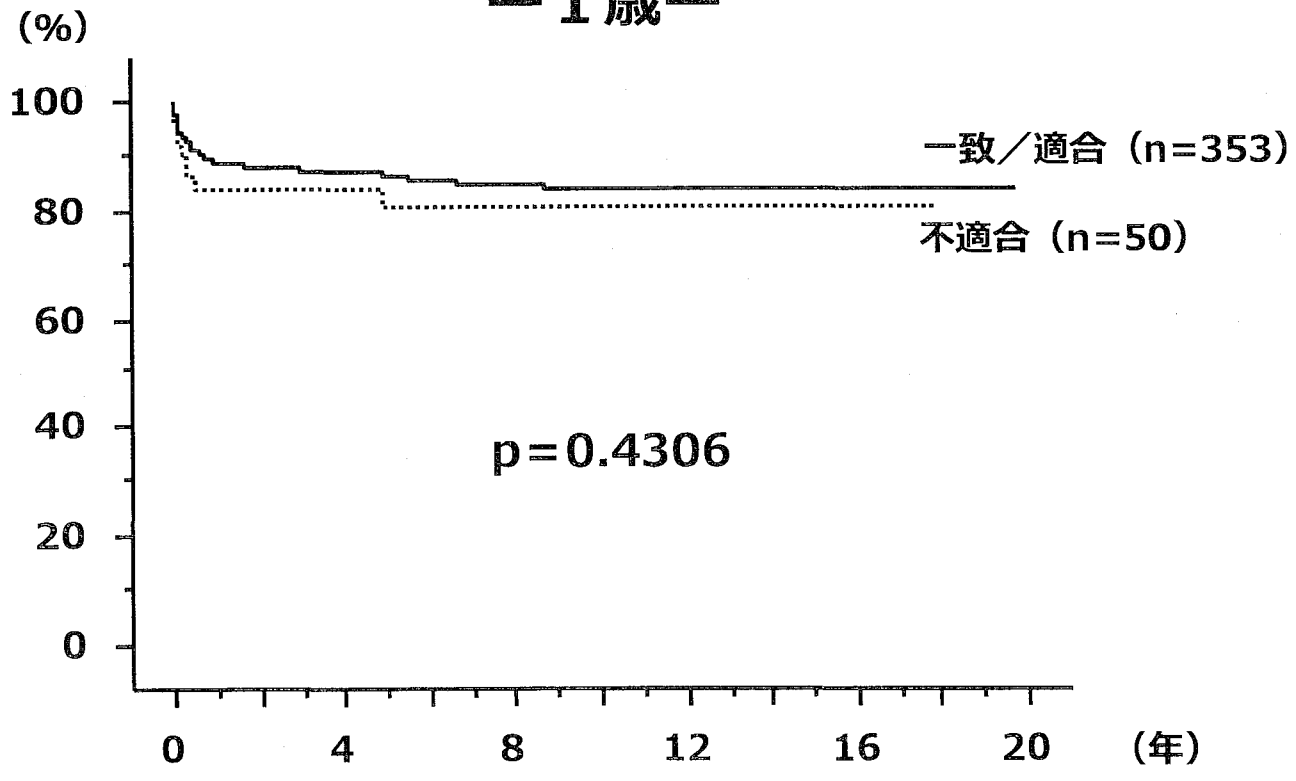


生体肝移植の ABO 血液型不適合群におけるレシピエント年齢別の累積生存率

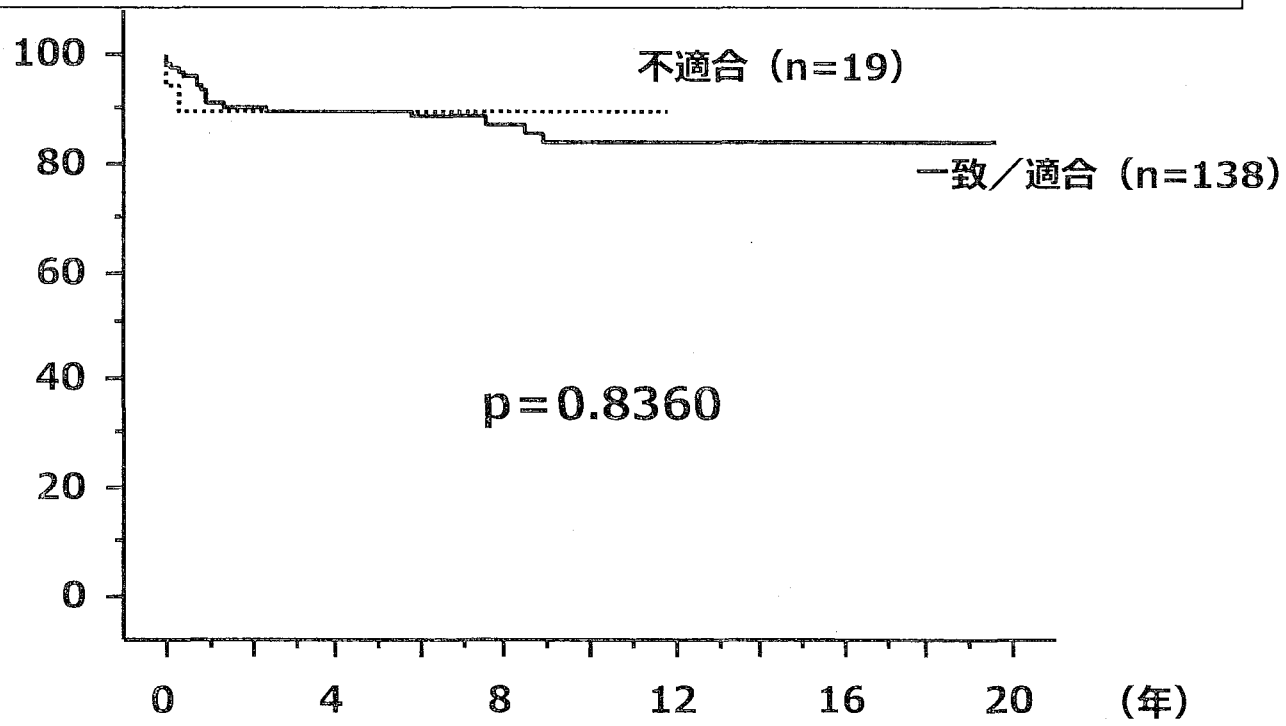
ＡＢＯ血液型適合度別の予後
－０歳－



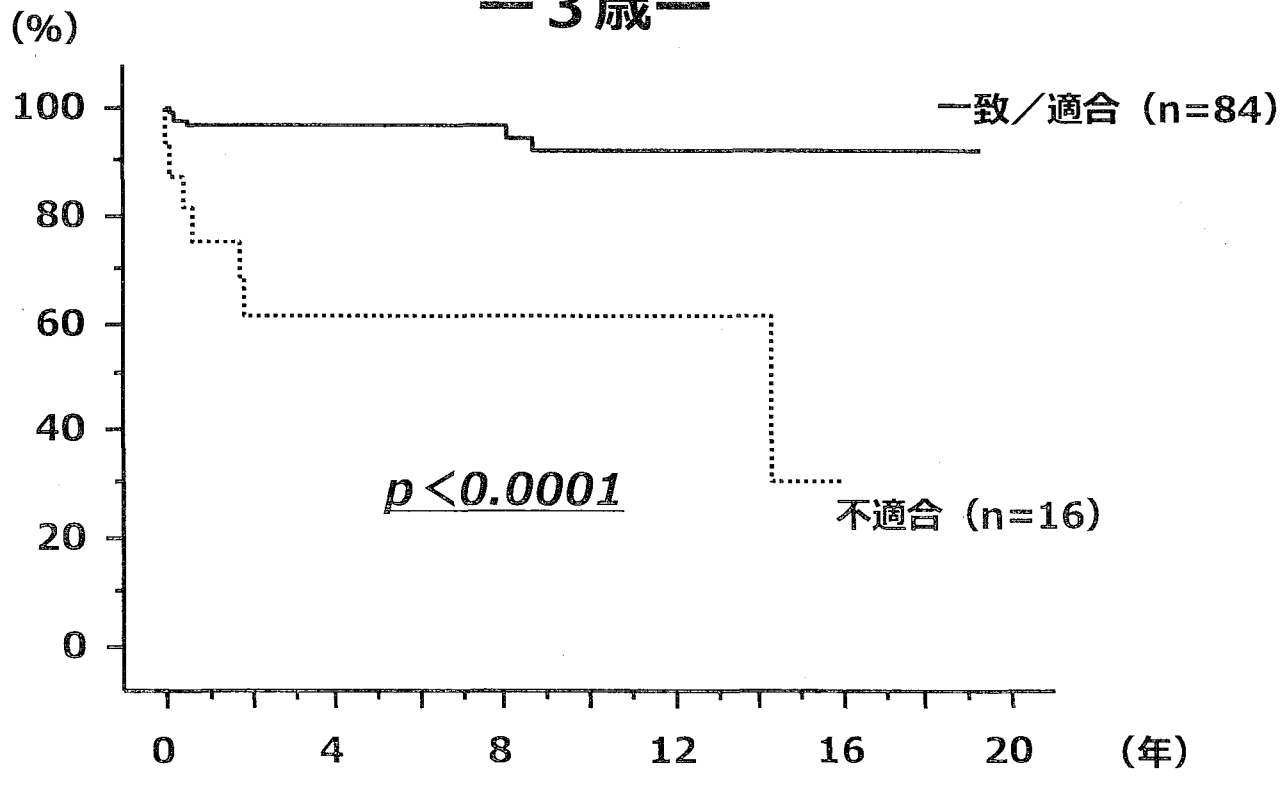
ＡＢＯ血液型適合度別の予後
－１歳－



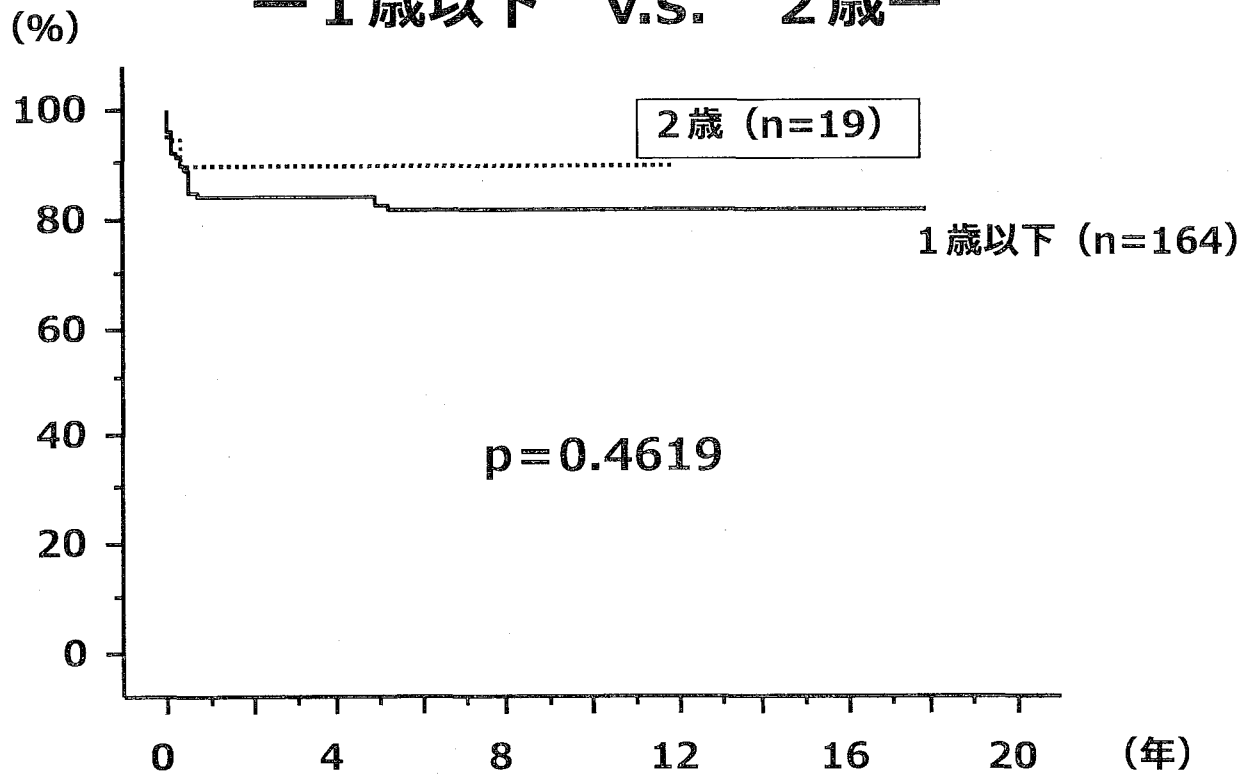
ＡＢＯ血液型適合度別の予後
－２歳－



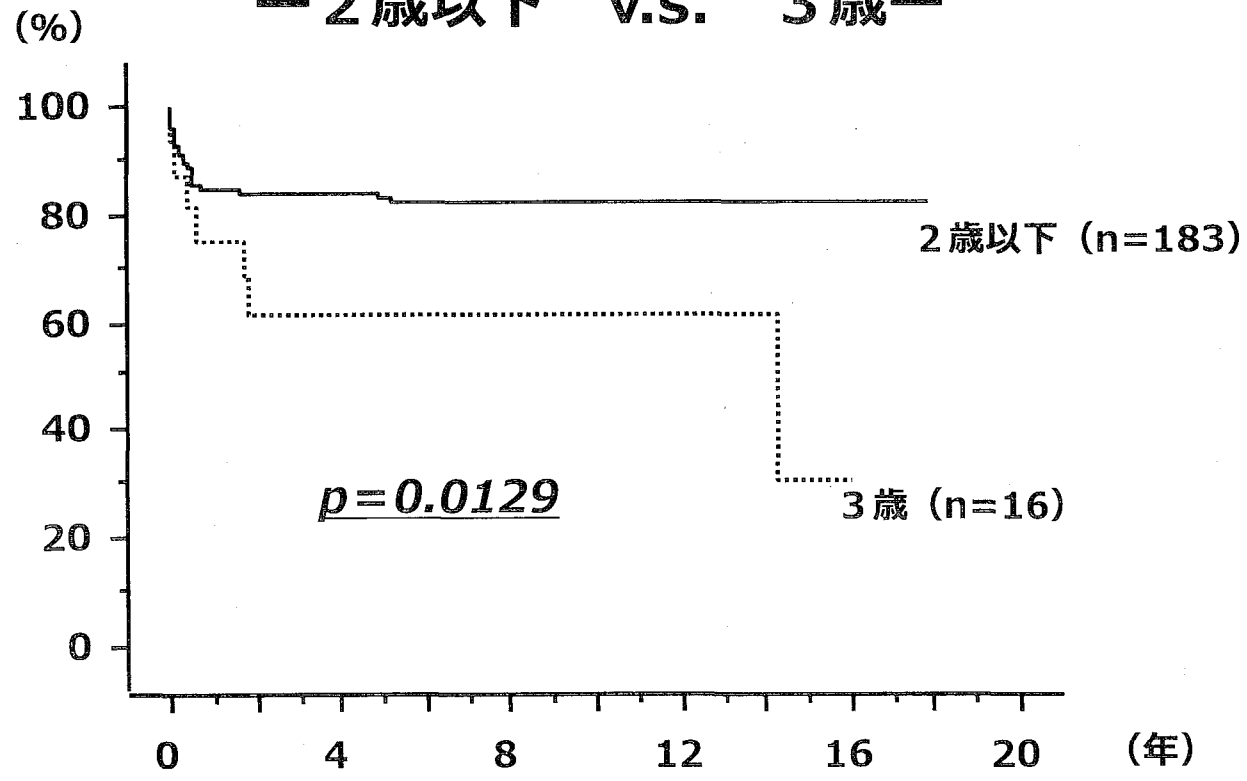
ＡＢＯ血液型適合度別の予後
－３歳－



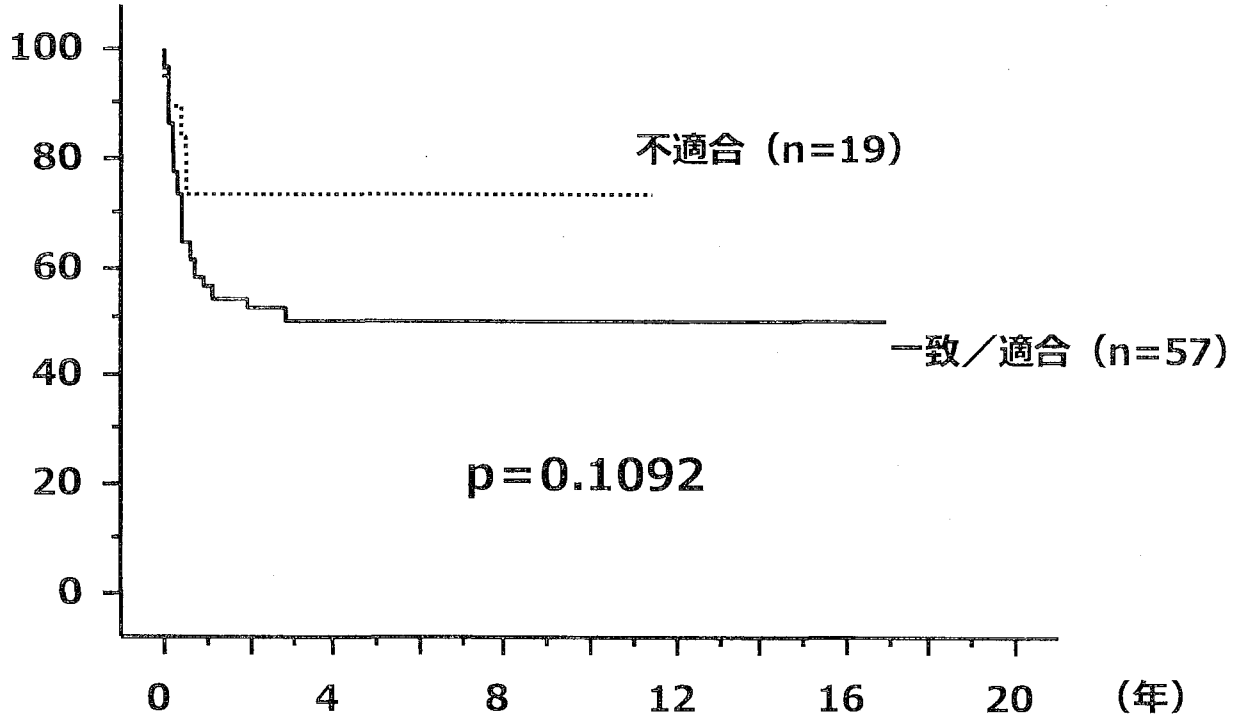
ＡＢＯ不適合肝移植の予後
－１歳以下　v.s.　２歳－



ＡＢＯ不適合肝移植の予後
－２歳以下　v.s.　３歳－



ＡＢＯ血液型適合度別の予後
－０歳、劇症肝炎のみ－



参考資料６

別紙

分割肝移植について

（公衆衛生審議会疾病対策部会
臓器移植専門委員会）

１　分割肝移植の実施

臓器の移植に関する法律（平成９年法律第１０４号）における脳死した者の身体からの肝臓移植に関し、当該肝臓を分割して移植すること（以下「分割肝移植」という。）については、第一選択の移植を受ける患者（以下「レシピエント」という。）が小児等であって、かつ、当該レシピエントに係る移植実施施設が、当該レシピエントに肝臓の一部を移植してもなお、残余の部分が移植に使用できる可能性があると判断したときに、その実施を考慮するものとする。

２　分割肝移植を実施する場合におけるドナーの望ましい状態等

分割肝移植を実施する場合には、全肝移植の肝臓と比べて肝臓の状態がよいことが求められることから、移植実施施設による分割肝移植の実施に当たっては、「臓器提供者（ドナー）適応基準及び移植希望者（レシピエント）選択基準について（平成９年１０月１６日健医発第１３７１号）」の「＜肝臓＞臓器提供者（ドナー）適応基準」に規定された条件等に加えて、臓器提供者（以下「ドナー」という。）が、以下の状態等にあることが望ましい。

１）６０歳以下であること。
２）循環動態が安定していること。
３）生化学的肝機能検査で著しい異常がないこと。
４）肉眼的に脂肪肝が認められないこと。
５）摘出前の循環管理において、ドナーに対して、カテコラミン等の強心薬が多量に使用されていないこと。（ドパミン及びドブタミンにあっては、１５γ（μｇ／ｋｇ／ｍｉｎ）以下であること。）

ただし、ドナーがこれらの状態等にない場合であっても、当該レシピエントの主治医が、医学的な観点から総合的に考慮して、移植を実施することが可能であると判断した場合にあっては、分割肝移植を実施することができる。

３　分割の方法

移植に用いられる肝臓を分割する方法については、ドナーの体内において分割する方法（以下「体内分割」という。）及びドナーの体外から肝臓を摘出した後に分割する方法（以下「体外分割」という。）の二種類があるが、移植成績等の観点から考慮すると、体内分割による場合の方が体外分割よりもすぐれていることから、原則として、体内分割によることが望ましい。ただし、多臓器が提供される場合における体内分割は、心臓、肺等の他の臓器に係る摘出チームと事前に調整し、体内分割の実施について合意が得られた場合に実施すること。

４　その他

なお、肝臓の移植を受けることとなる第一選択の患者が小児等である場合以外の分割肝移植の実施については、今後検討する。

（参考）

分割肝移植の流れについて

① 法的脳死判定開始

↓ 肝臓ドナー適応基準に従って評価

② 法的脳死判定終了

↓

③ レシピエントの選択

↓

④ 移植実施施設への連絡

レシピエントが小児等であった場合には、その移植実施施設に対して、当該レシピエントが移植を承諾する場合であって、分割肝移植実施の可能性があるときには、ネットワークにその旨を直ちに連絡するよう要請する。

↓

⑤ 小児等に対する分割肝移植の実施が確定

↓

⑥ 当該小児等の次順位以下のレシピエントに係る移植実施施設に対して、分割肝の移植の意思確認の連絡

↓ 一般の脳死下での肝臓移植と同様の手続で行う。

⑦ 当該残余の部分の肝臓のレシピエントが決定

↓

⑧ 摘出開始

多臓器が提供される場合であって、体内分割を実施するときは、心臓、肺など他の臓器に係る摘出チームと合意した上で体内分割を実施

↓

⑨ 摘出された肝臓の搬送及び移植手術の実施

1. ドナーとレシピエントの体重差に関するレシピエント選定基準について

移植ネットワーク	選定基準	参考文献
UNOS	記載無し	HP
Australia & NZ	記載無し	HP
Eurotransplant	記載無し	HP

2. 分割移植(Adult-to-adult)

	ドナー 適応	レシピ適応	ドナー・レシピ体重差	症例数	Split GRWR	Whole GRWR	患者生存率	胆管合併症	国	参考文献
1	記載無し	記載無し	基準無し	316	記載無し	記載無し	MELDで層別化:全肝移植(20778例)と同様	記載無し	ドイツ	Nadalin, et al. Transplant Int 2009:22:702-706
2	50歳未満、ICU<5daysなど	記載無し	基準無し	80	1.78(0.9-3.8)	2.36(1.2-3.9)	1年83%、5年82%:全肝移植89%、80%(80例)と同様	33%:全肝移植と同様	ドイツ	Takebe et al. Liver Transpl 2009:15;730-737
3	記載無し	GRWR0.7%<, PH軽度	基準無し	22	0.67-2.11	-	90%	4%	イタリア	Cescon et al. Transplantation 2009:88;1117-1122
4	記載無し	GRWR0.8%<	基準無し	31	記載無し	記載無し	3年74%:全肝移植74%(284例)と同様	全肝移植と同様	US	Humar et al. 2008:85;1420-1424
5	50歳未満、ICU<1w、良好なグラフトなど	サイズマッチ(詳細記載無し)・明らかなPH無し	基準無し	16	0.72-1.12	-	1年、3年、5年69%	25%	イタリア	Giaconomi A, et al. Liver Transpl 2008:14;999-1006
6	肉眼所見で特に問題なければ	全肝移植に同じ	基準無し	12	1.5	1.9	5年77%:全肝移植84%(12例)と同様	17%	ベルギー	Barriga et al. Clin Transplant 2008:22;447-455
7	50歳未満、ICU<5daysなど	初回移植など	基準無し	70	記載無し	記載無し	2年86%、5年78%:全肝移植(70例)と同様	11%:全肝移植と同様	ドイツ	Wilms et al. Ann Surg 2006:244;865-873

PH:Portal hypertension

参考資料7

参考資料８

小腸移植希望者（レシピエント）選択基準

１．適合条件

（１）ＡＢＯ式血液型

ＡＢＯ式血液型の一致（identical）及び適合（compatible）の待機者を候補者とする。

（２）体重（サイズ）

体重差は－５０％～２００％であることが望ましい。

（３）虚血許容時間

臓器提供者（ドナー）の小腸を摘出してから１２時間以内に血流再開することが望ましい。

（４）移植希望者（レシピエント）について

基礎疾患が良性疾患であること。

（５）CMV抗体

CMV抗体陰性の移植希望者（レシピエント）に対しては、CMV抗体陰性の臓器提供者（ドナー）が望ましい。

（６）前感作抗体及びＨＬＡ型

当面、選択基準にしないが、必ず検査し、登録する。

２．優先順位

適合条件に合致する移植希望者（レシピエント）が複数存在する場合には、優先順位は、以下の順に勘案して決定する。

（１）親族

臓器の移植に関する法律第６条の２の規定に基づき、親族に対し臓器を優先的に提供する意思が表示されていた場合には、当該親族を優先する。

ただし、ＨＬＡの適合度を必ず確認し、臓器提供者（ドナー）のＨＬＡ—Ａ、ＨＬＡ—Ｂ、ＨＬＡ—ＤＲのすべてにホモ接合体が存在し、移植希望者（レシピエント）が臓器提供者（ドナー）のハプロタイプを共有するヘテロ接合体である場合には、移植片対宿主病（ＧＶＨＤ）の危険性が高いため、除く。

（2）医学的緊急度（Status１を最優先とし、次にStatus２、Status３の順に優先する。）

Status１：中心静脈栄養法の維持が不可能になった状態

Status２：血清ビリルビン値の高値持続と、肝臓障害が進行しつつある状態

Status３：中心静脈栄養法の維持が不可能となりつつある状態

（3）ＡＢＯ式血液型

ＡＢＯ式血液型の一致（identical）する者を適合（compatible）する者より優先する。

（4）待機期間

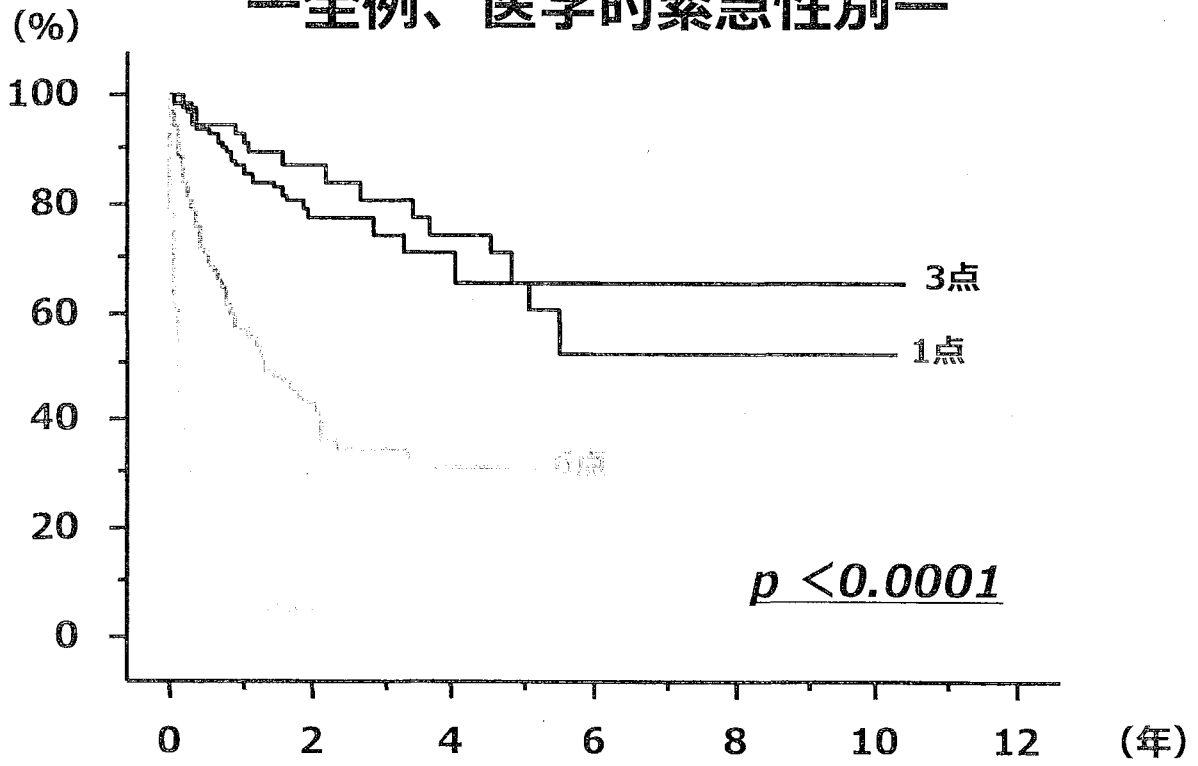
待機期間の長い者を優先する。

3．その他

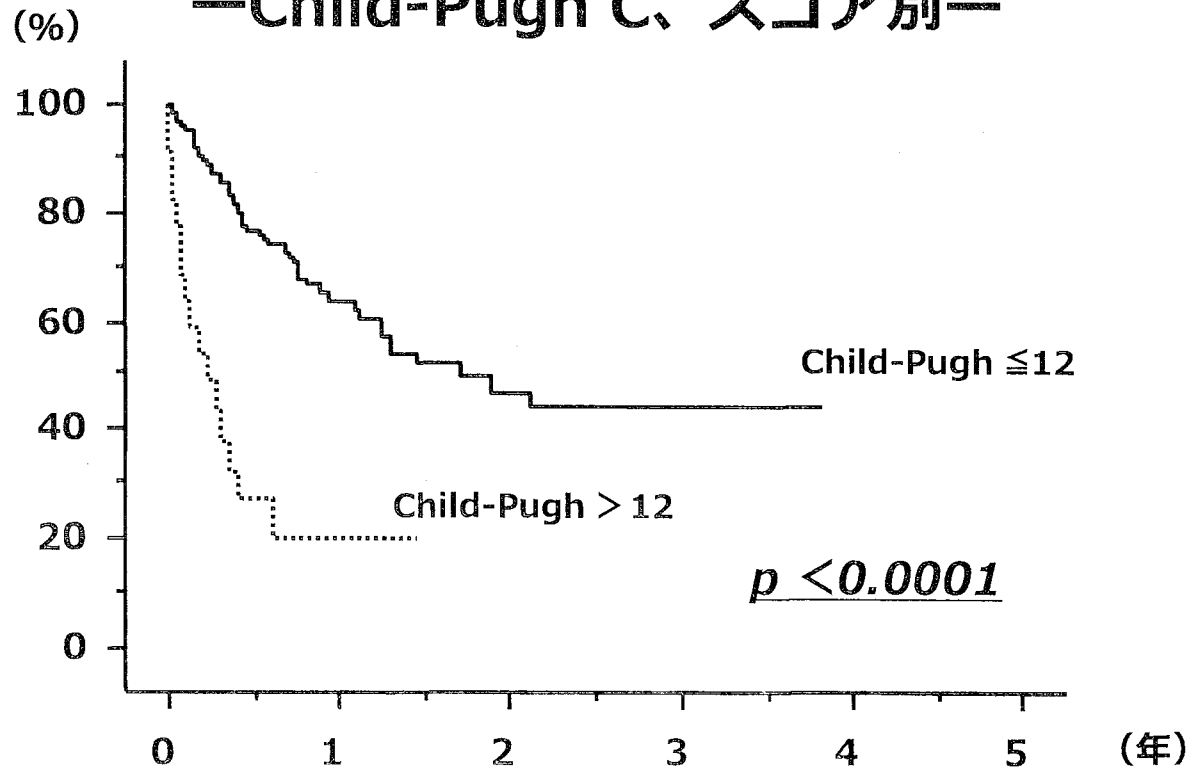
基準全般については、今後の移植医療の定着及び移植実績の評価等を踏まえ、適宜見直すこととする。

参考資料９

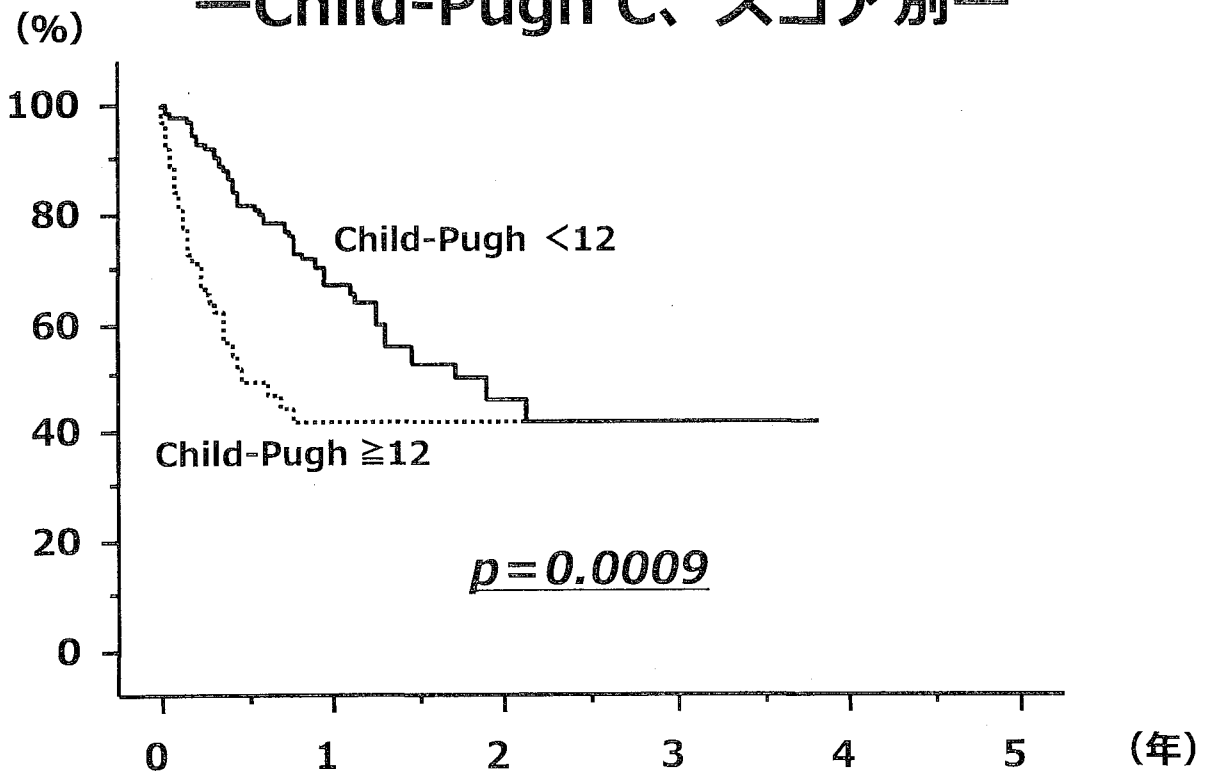
適応評価後の予後
―全例、医学的緊急性別―



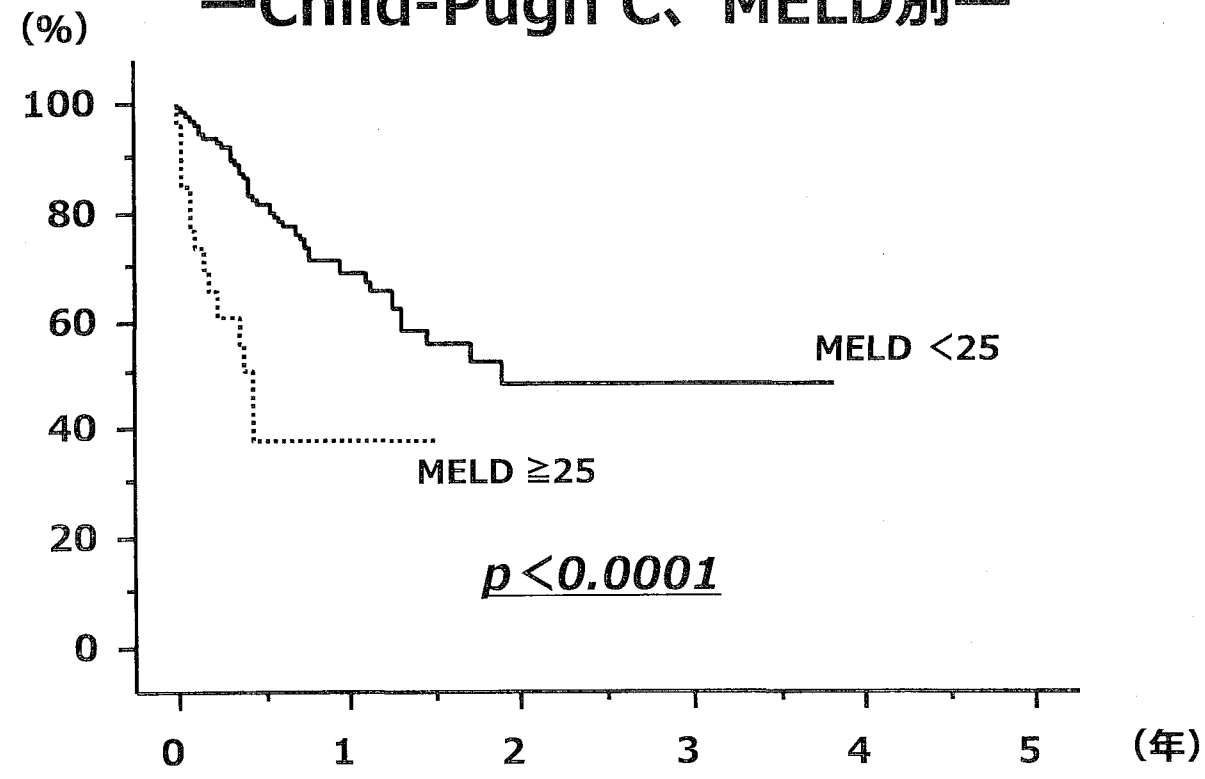
適応評価後の予後
―Child-Pugh C、スコア別―



適応評価後の予後
—Child-Pugh C、スコア別—



適応評価後の予後
—Child-Pugh C、MELD別—



適応評価後の予後
—Child-Pugh C、MELD別—