donation. Measures should be taken to remove obstacles and disincentives to deceased organ donation.

(2) In countries without established deceased organ donation or transplantation, national legislation should be enacted that would initiate deceased organ donation and create transplantation infrastructure, so as to fulfill each country's deceased donor potential.

(3) In all countries in which deceased organ donation has been initiated, the therapeutic potential of deceased organ donation and transplantation should be maximized.

(4) Countries with well-established deceased donor transplant programs are encouraged to share information, expertise, and technology with countries seeking to improve their organ donation efforts.

To ensure the protection and safety of living donors and appropriate recognition for their heroic act while combating transplant tourism, organ trafficking and transplant commercialism:

(1) The act of donation should be regarded as heroic and honored as such by representatives of the government and civil society organizations.

(2) The determination of the medical and psychosocial suitability of the living donor should be guided by the recommendations of the Amsterdam and Vancouver Forums.[2–4]
   (a) Mechanisms for informed consent should incorporate provisions for evaluating the donor's understanding, including assessment of the psychological impact of the process.
   (b) All donors should undergo psychosocial evaluation by mental health professionals during screening.

(3) The care of organ donors, including those who have been victims of organ trafficking, transplant commercialism, and transplant tourism, is a critical responsibility of all jurisdictions that sanctioned organ transplants utilizing such practices.

(4) Systems and structures should ensure standardization, transparency, and accountability of support for donation.
   (a) Mechanisms for transparency of process and follow-up should be established.
   (b) Informed consent should be obtained both for donation and for follow-up processes.

(5) Provision of care includes medical and psychosocial care at the time of donation and for any short- and long-term consequences related to organ donation.
   (a) In jurisdictions and countries that lack universal health insurance, the provision of disability, life, and health insurance related to the donation event is a necessary requirement in providing care for the donor.
   (b) In those jurisdictions that have universal health insurance, governmental services should ensure donors have access to appropriate medical care related to the donation event.
   (c) Health and/or life insurance coverage and employment opportunities of persons who donate organs should not be compromised.
   (d) All donors should be offered psychosocial services as a standard component of follow-up.
   (e) In the event of organ failure in the donor, the donor should receive the following:
      (i) Supportive medical care, including dialysis for those with renal failure, and
      (ii) Priority for access to transplantation, integrated into existing allocation rules as they apply to either living or deceased organ transplantation.

(6) Comprehensive reimbursement of the actual, documented costs of donating an organ does not constitute a payment for an organ, but is rather part of the legitimate costs of treating the recipient.
   (a) Such cost reimbursement would usually be made by the party responsible for the costs of treating the transplant recipient (such as, a government health department or a health insurer).
   (b) Relevant costs and expenses should be calculated and administered using transparent methodology, consistent with national norms.
   (c) Reimbursement of approved costs should be made directly to the party supplying the service (such as, to the hospital that provided the donor's medical care).
   (d) Reimbursement of the donor's lost income and out-of-pocket expenses should be administered by the agency handling the transplant rather than paid directly from the recipient to the donor.

(7) Legitimate expenses that may be reimbursed when documented include the following:
   (a) The cost of any medical and psychological evaluations of potential living donors who are excluded from donation (e.g., because of medical or immunologic issues discovered during the evaluation process).
   (b) Costs incurred in arranging and effecting the pre-, peri-, and postoperative phases of the donation process (e.g., long-distance telephone calls, travel, accommodation, and subsistence expenses).
   (c) Medical expenses incurred for post-discharge care of the donor.
   (d) Lost income in relation to donation (consistent with national norms).

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APPENDIX Process and Participant Selection

Steering Committee

The Steering Committee was selected by an Organizing Committee consisting of Mona Alrukhami, Jeremy Chapman, Francis Delmonico, Mohamed Sayegh, Faissal Shaheen, and Annika Tibell.

The Steering Committee was composed of leadership from The Transplantation Society, including its President-elect and the Chair of its Ethics Committee, and the International Society of Nephrology, including its Vice President and individuals holding Council positions. The Steering Committee had representation from each of the continental regions of the globe with transplantation programs.

The mission of the Steering Committee was to draft a Declaration for consideration by a diverse group of participants at the Istanbul Summit. The Steering Committee also had the responsibility to develop the list of participants to be invited to the Summit meeting.

Istanbul Participant Selection

Participants at the Istanbul Summit were selected by the Steering Committee according to the following considerations:

- The country liaisons of The Transplantation Society representing virtually all countries with transplantation programs;
- Representatives from international societies and the Vatican;
- Individuals holding leadership positions in nephrology and transplantation;
- Stakeholders in the public policy aspect of organ transplantation; and
- Ethicists, anthropologists, sociologists, and legal scholars well recognized for their writings regarding transplantation policy and practice.

No person or group was polled with respect to their opinion, practice, or philosophy prior to the Steering Committee selection or the Istanbul Summit.

After the proposed group of participants was prepared and reviewed by the Steering Committee, they were sent a letter of invitation to the Istanbul Summit, which included the following components:

- the mission of the Steering Committee to draft a Declaration for all Istanbul participants' consideration;
- the agenda and work group format of the Summit;
- the procedure for the selection of participants;
- the work group topics;
- an invitation to the participants to indicate their work group preferences;
- the intent to communicate a draft and other materials before the Summit convened;
- the Summit goals to assemble a final declaration that could achieve consensus and would address the issues of organ trafficking, transplant tourism and commercialism, and provide principles of practice and recommended alternatives to address the shortage of organs;
- an acknowledgment of the funding provided by Astellas Pharmaceuticals for the Summit;
- provision of hotel accommodations and travel for all invited participants.

Of approximately 170 persons invited, 160 agreed to participate and 152 were able to attend the Summit in Istanbul on 30 April to 2 May 2008. Because work on the Declaration at the Summit was to be carried out by dividing the draft document into separate parts, Summit invitees were assigned to a work group topic based on their response concerning the particular topics on which they wished to focus their attention before and during the Summit.

Preparation of the Declaration

The draft Declaration prepared by the Steering Committee was furnished to all participants with ample time for appraisal and response prior to the Summit. The comments and suggestions received in advance were reviewed by the Steering Committee and given to leaders of the appropriate work group at the Summit. (Work group leaders were selected and assigned from the Steering Committee.)

The Summit meeting was formatted so that breakout sessions of the work groups could consider the written responses received from participants prior to the Summit as well as comments from each of the work group participants. The work groups elaborated these ideas as proposed additions to and revisions of the draft. When the Summit reconvened in plenary session, the Chairs of each work group presented the outcome of their breakout session to all Summit participants for discussion. During this process of review, the wording of each section of the Declaration was displayed on a screen before the plenary participants and was modified in light of their comments until consensus was reached on each point.

The content of the Declaration is derived from the consensus that was reached by the participants at the Summit in the plenary sessions which took place on 1 and 2 May 2008. A formatting group was assembled immediately after the Summit to address punctuation, grammatical, and related concerns and to record the Declaration in its finished form.

Participants in the Istanbul Summit

Last name	First name	Country
Abboud	Omar	Sudan
Abbud-Filho[a]	Mario	Brazil
Abdramanov	Kaldarbek	Kyrgyzstan
Abdulla	Sadiq	Bahrain
Abraham	Georgi	India
Abueva	Amihan V.	Philippines
Aderibigbe	Ademola	Nigeria
Al-Mousawi[a]	Mustafa	Kuwait
Alberu	Josefina	Mexico
Allen	Richard D.M.	Australia
Almazan-Gomez	Lynn C.	Philippines
Alnono	Ibrahim	Yemen
Alobaidli[a]	Ali Abdulkareem	United Arab Emirates
Alrukhaimi[a]	Mona	United Arab Emirates
Álvarez	Inés	Uruguay
Assad	Lina	Saudi Arabia
Assounga	Alain G.	South Africa
Baez	Yenny	Colombia
Bagheri[a]	Alireza	Iran
Bakr[a]	Mohamed Adel	Egypt
Bamgboye	Ebun	Nigeria
Barbari[a]	Antoine	Lebanon
Belghiti	Jacques	France
Ben Abdallah	Taieb	Tunisia
Ben Ammar	Mohamed Salah	Tunisia
Bos	Michael	The Netherlands
Britz	Russell	South Africa
Budiani	Debra	Untied States
Capron[a]	Alexander	Untied States
Castro	Cristina R.	Brazil
Chapman[a]	Jeremy	Australia
Chen	Zhonghua Klaus	People's Republic of China
Codreanu	Igor	Moldova
Cole	Edward	Canada
Cozzi	Emanuele	Italy
Danovitch[a]	Gabriel	Untied States
Davids	Razeen	South Africa
De Broe	Marc	Belgium
De Castro[a]	Leonardo	Philippines
Delmonico[a]	Francis L.	Untied States
Derani	Rania	Syria
Dittmer	Ian	New Zealand
Domínguez-Gil	Beatriz	Spain
Duro-Garcia	Valter	Brazil
Ehtuish	Ehtuish	Libya
El-Shoubaki	Hatem	Qatar
Epstein	Miran	United Kingdom
Fazel[a]	Iraj	Iran
Fernandez Zincke	Eduardo	Belgium
Garcia-Gallont	Rudolf	Guatemala
Ghods	Ahad J.	Iran
Gill	John	Canada
Glotz	Denis	France
Gopalakrishnan	Ganesh	India
Gracida	Carmen	Mexico
Grinyo	Josep	Spain
Ha	Jongwon	South Korea
Haberal[a]	Mehmet A.	Turkey
Hakim	Nadey	United Kingdom
Harmon	William	Untied States
Hasegawa	Tomonori	Japan
Hassan	Ahmed Adel	Egypt
Hickey	David	Ireland
Hiesse	Christian	France
Hongji	Yang	People's Republic of China
Humar	Ines	Croatia
Hurtado	Abdias	Peru

Continued

Last name	First name	Country
Ismail Moustafa	Wesam	Egypt
Ivanovski	Ninoslav	Macedonia
Jha[a]	Vivekanand	India
Kahn	Delawir	South Africa
Kamel	Refaat	Egypt
Kirpalani	Ashok	India
Kirste	Guenter	Germany
Kobayashi[a]	Eiji	Japan
Koller	Jan	Slovakia
Kranenburg	Leonieke	The Netherlands
Lameire[a]	Norbert	Belgium
Laouabdia-Sellami	Karim	France
Lei	Ruipeng	People's Republic of China
Levin[a]	Adeera	Canada
Lloveras	Josep	Spain
Lõhmus	Aleksander	Estonia
Luciolli	Esmeralda	France
Lundin	Susanne	Sweden
Lye	Wai Choong	Singapore
Lynch	Stephen	Australia
Maïga[a]	Mahamane	Mali
Mamzer Bruneel	Marie-France	France
Maric	Nicole	Austria
Martin[a]	Dominique	Australia
Masri[a]	Marwan	Lebanon
Matamoros	Maria A.	Costa Rica
Matas	Arthur	Untied States
McNeil	Adrian	United Kingdom
Meiser	Bruno	Germany
Meši	Enisa	Bosnia
Moazam	Farhat	Pakistan
Mohsin	Nabil	Oman
Mor	Eytan	Israel
Morales	Jorge	Chile
Munn	Stephen	New Zealand
Murphy	Mark	Ireland
Naicker[a]	Saraladevi	South Africa
Naqvi	S.A. Anwar	Pakistan
Noël[a]	Luc	World Health Organization
Obrador	Gregorio	Mexico
Oliveros	Yolanda	Philippines
Ona	Enrique	Philippines
Oosterlee	Arie	The Netherlands
Oyen	Ole	Norway
Padilla	Benita	Philippines
Pratschke	Johann	Germany
Rahamimov	Ruth	Israel
Rahmel	Axel	The Netherlands
Reznik	Oleg	Russia
Rizvi[a]	S. Adibul Hasan	Pakistan
Roberts	Lesley Ann	Trinidad and Tobago
Rodriguez-Iturbe[a]	Bernardo	Venezuela
Rowinski	Wojciech	Poland
Saeed	Bassam	Syria
Sarkissian	Ashot	Armenia
Sayegh[a]	Mohamed H.	Untied States
Scheper-Hughes	Nancy	Untied States
Sever	Mehmet Sukru	Turkey
Shaheen[a]	Faissal A.	Saudi Arabia
Sharma	Dhananjaya	India
Shinozaki	Naoshi	Japan
Simforoosh	Nasser	Iran
Singh	Harjit	Malaysia
Sok Hean	Thong	Cambodia
Somerville	Margaret	Canada
Stadtler	Maria	Untied States
Stephan[a]	Antoine	Lebanon

Continued

Last name	First name	Country
Suárez	Juliette	Cuba
Suaudeau	Msgr. Jacques	Italy
Sumethkul	Vasant	Thailand
Takahara	Shiro	Japan
Thiel	Gilbert T.	Switzerland
Tibell[a]	Annika	Sweden
Tomadze	Gia	Georgia
Tong[a]	Matthew Kwok-Lung	Hong Kong
Tsai	Daniel Fu-Chang	Taiwan
Uriarte	Remedios	Philippines
Vanrenterghem	Yves F.C.	Belgium
Vathsala[a]	A.	Singapore
Weimar	Willem	The Netherlands
Wikler	Daniel	Untied States
Young	Kimberly	Canada
Yuldashev	Ulugbek	Uzbekistan
Zhao	Minggang	People's Republic of China

[a]Members of the Steering Committee. (William Couser, USA, was also a member of the Steering Committee but was unable to attend the Summit.)

Organ trafficking and transplant tourism and commercialism: the Declaration of Istanbul

Organ trafficking, transplant tourism, and transplant commercialism, which threaten to undermine the practice of transplantation worldwide, were the focus of an international summit in Istanbul from April 30 to May 1, 2008. The summit was convened by The Transplantation Society and the International Society of Nephrology. The meeting resulted in the *Declaration of Istanbul on Organ Trafficking and Transplant Tourism* (webappendix), which aims to halt these unethical activities and to foster safe and accountable practices that meet the needs of transplant recipients while protecting donors.

The initial text of the declaration was prepared by a steering committee, which also invited medical and scientific professionals, representatives of governmental and social agencies, social scientists, legal scholars, and ethicists to participate in the meeting. None of the 152 participants from 78 countries was polled with respect to his or her opinion, practice, or philosophy before selection. The declaration was agreed by consensus among the summit's participants.

For more than two decades, governments around the world have recognised the need to protect poor people from the exploitation inherent in organ sales.[1–4] Yet, partly as a consequence of the widespread shortage of organs and the increasing ease of internet communication, organ trafficking and transplant tourism have become global problems. Vulnerable populations (such as illiterate and impoverished individuals, undocumented immigrants, prisoners, and political or economic refugees) in resource-poor countries are now a major source of organs for rich patient-tourists who are prepared to travel and can afford to purchase organs.[5] WHO has estimated that about 10% of organ transplants around the world involve these unacceptable activities and in some countries the rate is much higher (Noël L, WHO, Geneva, Switzerland; personal communication). For example, by 2006, two-thirds of the 2000 kidney transplants in Pakistan were for foreign recipients.[6]

An essential first step in combating such activities is to describe them precisely. The declaration clearly defines organ trafficking, transplant commercialism, and transplant tourism (panel). The declaration also proposes policies and principles of practice on the basis of the definitions: "Organ trafficking and transplant tourism violate the principles of equity, justice and respect for human dignity and should be prohibited. Because transplant commercialism targets impoverished and otherwise vulnerable donors, it leads inexorably to inequity and injustice and should also be prohibited." To be effective, these prohibitions must include bans on all types of advertising (electronic and print), soliciting, or brokering for the purpose of transplant commercialism.

See Online for webappendix

The declaration describes universal approaches for the provision of care for the living donor, and also emphasises the need for effective practices that support organ donation from dead donors. Reimbursement of the documented costs incurred during the evaluation and performance of the donor procedure is part of the legitimate expense of transplantation and does not constitute a payment for organs. Governments should ensure the provision of care and follow-up of living donors, which should be no less than the care and attention provided for transplant recipients. For example, the provision of disability, life, and health insurance related to the donation event is an essential part of providing care for the donor in countries without social insurance systems.

Countries from which transplant tourists originate, as well as those to which they travel to obtain

***Panel:* Definitions from the Declaration of Istanbul on Organ Trafficking and Transplant Tourism**

Organ trafficking is the recruitment, transport, transfer, harbouring, or receipt of living or deceased persons or their organs by means of the threat or use of force or other forms of coercion, of abduction, of fraud, of deception, of the abuse of power or of a position of vulnerability, or of the giving to, or the receiving by, a third party of payments or benefits to achieve the transfer of control over the potential donor, for the purpose of exploitation by the removal of organs for transplantation.

Transplant commercialism is a policy or practice in which an organ is treated as a commodity, including by being bought or sold or used for material gain.

Travel for transplantation is the movement of organs, donors, recipients, or transplant professionals across jurisdictional borders for transplantation purposes. Travel for transplantation becomes **transplant tourism** if it involves organ trafficking and/or transplant commercialism or if the resources (organs, professionals, and transplant centres) devoted to providing transplants to patients from outside a country undermine the country's ability to provide transplant services for its own population.

transplants, are just beginning to address their respective responsibilities to protect their people from exploitation and to develop a national self-sufficiency in organ donation. Leadership and encouragement from transplant professionals would contribute greatly to governments taking effective action to adopt and then to enforce strong laws consistent with the declaration. Participants in the Istanbul meeting have already played major roles in the promulgation of such laws and regulations within the past 2 years in China, Pakistan, and the Philippines.

The implications of the declaration's definitions, principles, and recommendations are profound. The declaration will reinforce the resolve of governments and international organisations to develop laws and guidelines to bring an end to wrongful practices. The declaration calls for transparent regulatory oversight—with international accountability—that ensures the safety and wellbeing of donors and recipients alike.

Still, more is needed from the transplant and medical communities. The Transplantation Society and the International Society of Nephrology have endorsed the declaration. The steering committee has created task forces to facilitate dissemination of the declaration to national health authorities and to supplement existing professional standards. Recommendations from these task forces ought to include cancelling the professional society membership of individuals who do not adhere to the principles of the declaration. Drug companies and other funding agencies ought to apply the declaration's principles when supporting research and other clinical activities. Journals ought not to publish studies from individuals or groups who do not comply with the declaration.

The legacy of transplantation is threatened by organ trafficking and transplant tourism. The *Declaration of Istanbul on Organ Trafficking and Transplant Tourism* aims to combat these activities and to preserve the nobility of organ donation. The success of transplantation as a life-saving treatment does not require—nor justify—victimising the world's poor people as the source of organs for the rich.

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@ Selective factor Xa inhibition for thromboprophylaxis

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See **Articles** page 31

For over 60 years, vitamin K antagonists, such as warfarin, have been the only available oral anticoagulants. Although effective, these drugs are challenging to use. Dose requirements vary among patients and the anticoagulant response is unpredictable. Consequently, coagulation needs to be monitored and the dose frequently adjusted to ensure that a therapeutic level of anticoagulation is achieved. Such monitoring is inconvenient for patients and costly for health-care systems.

特集◇生体移植医療の実際

生体肝移植

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Key words：生体肝移植，適応疾患，生体ドナー

Ⅰ．生体肝移植の歴史と本邦の現状

1963年にアメリカのStarzlにより胆道閉鎖症の患児に対して世界初の死体肝移植が行われた後，1980年代には，免疫抑制剤cyclosporineの応用により臓器移植の成績が飛躍的に向上した。しかし，当時より小児への移植肝は不足しており，これを解消する目的で1988年にブラジルのRaiaら[1]によって世界初の生体肝移植が胆道閉鎖症患児に対して行われ，わが国でも1989年の島根医科大学での第1例目を皮切りに各施設で行われるようになった。当初はドナーの危険性が少ない左外側区域グラフトを用いる小児例に対して施行されたが，1993年信州大学で左葉グラフトを用いた世界初の成人生体肝移植の成功[2]以降，さらに手術手技・免疫抑制療法・周術期管理などの技術革新により成人症例が増加し，そして1998年頃より右葉グラフトが導入されるようになってから成人への適応がさらに拡大し，現在では成人症例が生体肝移植全体の約2/3を占めている。一方，1997年に臓器移植法がわが国でも成立し脳死肝移植の普及が期待されたが，脳死ドナーの発生は少なく実際に施行されたのは2008年末現在まで合計58例にすぎない。そのため現在もドナー不足は深刻であり，生体肝移植への需要がますます拡大する傾向にある。本邦においては，2001年以降毎年400例を超える生体肝移植が行われており，その総数は2007年末までで4,725例に至っている。

Ⅱ．適応疾患の拡大と適応評価

現在本邦における生体肝移植の適応疾患は多岐にわたっており（**表1**），小児では胆道閉鎖症が大半を占めているのに対して，成人においては胆汁うっ滞性疾患の他，肝細胞癌やC型肝硬変に対する移植件数の割合が特に増加している（**図1，2**）[3]。適応外病態としては，1）制御不能な肝外悪性新生物の合併，2）アルコールを含めた薬物依存，3）重度肺高血圧症，4）制御不能の感染症，などがある。

A．移植適応のタイミング

肝硬変症においては，移植後生存率が保存的治療にて見込まれる予後よりも上回る場合に肝移植を考慮する。肝硬変の進行に伴い，利尿剤にてコントロール困難な難治性腹水・頻回の肝性脳症・食道静脈瘤破裂などの症状が認められた場合は早急な対応が必要である。一般的にはChild-Pughスコアと Model for Endstage Liver Disease（MELD）スコアなどが適応時期を

表 1 生体部分肝移植の保険適応疾患（2004年1月改訂）

- 先天性胆道閉鎖症
- 進行性肝内胆汁うっ滞症
  （原発性胆汁性肝硬変と原発性硬化性胆管炎を含む）
- Alagille 症候群
- Budd-Chiari 症候群
- 先天性代謝性肝疾患（家族性アミロイドポリニューロパチーを含む）
- 多発嚢胞肝
- カロリ病
- 非代償性肝硬変
- 劇症肝炎（ウイルス性，自己免疫性，薬剤性，成因不明を含む）
- 肝硬変合併肝細胞癌
  （遠隔転移と血管侵襲を認めないもので，肝内に径5 cm 以下1個，または径3 cm 以下3個以内が存在する場合）

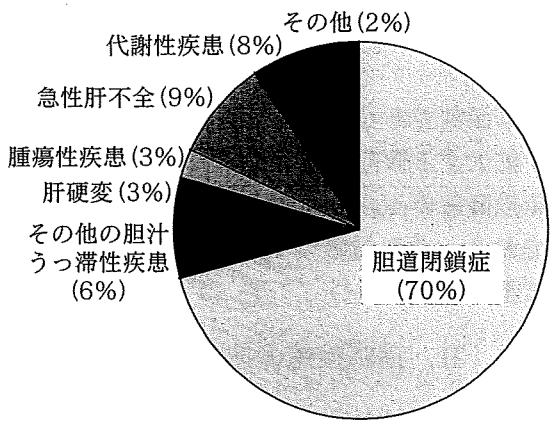

図 1 適応疾患（小児：18歳未満，初回移植）[n=1,735]

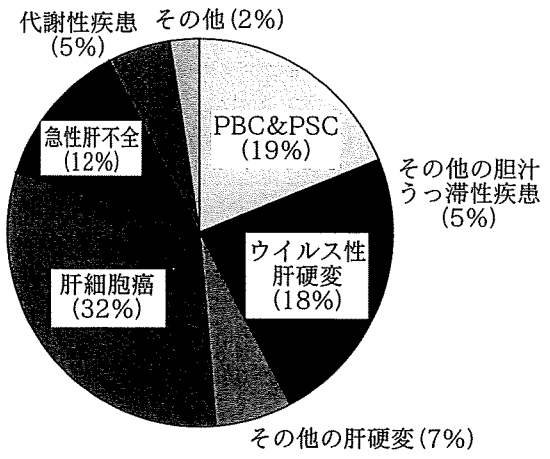

図 2 適応疾患（成人：18歳以上，初回移植）[n=2,868]

判定する際に用いられることが多い。Child-Pugh スコアは肝硬変の病期分類（A～C）として開発されたもので，アルブミン・ビリルビン・プロトロンビン時間・腹水・肝性脳症の5項目を用いてスコアリングし，病期分類Cとなると非代償期として肝移植を考慮する時期とされる。MELD スコアはクレアチニン・ビリルビン・プロトロンビン時間（INR）により6から40にスコア化し，非代償性肝硬変患者における保存的治療時の死亡率を予測するものであるが[4)5)]，15点以上で肝移植を考慮する時期であり，20点以上では早急に肝移植が必要と考えられている。

B．胆汁うっ滞性疾患に対する生存予測モデル（表2）

原発性胆汁性肝硬変（PBC）および原発性硬化性胆管炎（PSC）については至適時期での肝移植を目的として生存予測が詳細に検討されてきた。PBC の予後予測モデルには日本肝移植適応研究会モデルおよび Mayo Clinic の Updated model[6)] がある。欧米では6カ月生存率が50%を下回った場合に移植適応時期とされている[7)]。一方 PSC では Update Mayo Model[8)] が用いられ，High risk group で移植適応と考えられているが，胆管炎の程度や QOL なども適応を決める上で重要である。また PSC には

表 2 生存予測モデル

[原発性胆汁性肝硬変]

I. Mayo Updated Model (1994)

6カ月後生存率$=0.992^{(R-6.119)}$

$R=0.051\times$(年齢)$+1.209\times\log_e$[総ビリルビン(mg/dl)]$+2.754\times\log_e$[プロトロンビン時間(秒)]
$-3.304\times\log_e$[アルブミン(g/dl)]$+0.675\times$(浮腫の有無：0 or 0.5 or 1.0)

浮腫の有無　0：浮腫がなく利尿剤投与もなし
0.5：浮腫を認めるが利尿剤にて消失する
1.0：浮腫を認め，利尿剤でも消失しない

II. 日本肝移植適応研究会モデル

6カ月後予測死亡率$=1/(1+e^{-\lambda})$

$\lambda=-4.333+1.2739\times\log_e$[ビリルビン(mg/dl)]$+4.488\times\log_e$(GOT/GPT)

[原発性硬化性胆管炎]

Updated Mayo Model (1999)

{Mayo Risk Score}

$R=0.03\times$(年齢)$+0.54\times\log_e$[総ビリルビン(mg/dl)] $-0.84\times$[アルブミン(g/dl)]
$+0.54\times\log_e$[AST(IU/l)]$+1.24\times$[静脈瘤出血の有無(yes：1, no：0)]

低リスク：R=or<0，中等度リスク：0<R<2.0，高リスク：R=or>2.0

表 3 劇症肝炎における肝移植適応のガイドライン（日本急性肝不全研究会，1996）

I. 脳症発現時に次の5項目のうち2項目を満たす場合は死亡と予測して肝移植の登録を行う
1. 年齢：45歳以上
2. 亜急性型（初発症状から脳症発現までの日数：11日以上）
3. プロトロンビン時間：10%未満
4. 血清総ビリルビン濃度：18 mg/dl以上
5. 直接/総ビリルビン比：0.67以下

II. 治療開始（脳症発現）から5日後における予後の再予測
1. 脳症がI度以内に覚醒，あるいは昏睡度でII度以上の改善
2. プロトロンビン時間が50%以上に改善

以上のうちで，認められる項目数が
2項目以上の場合：生存と予測して肝移植の登録を取り消す
0または1項目の場合：死亡と再予測して肝移植の登録を継続する

悪性疾患の合併が15～30%に認められることが知られているが[9]，胆管癌を合併したPSCに対する移植は禁忌と考えられているため，悪性疾患を疑う場合は肝生検やERCP下の生検・細胞診などを積極的に行うべきである。

C．劇症肝炎に対する移植適応

劇症肝炎は内科的治療に抵抗性の場合に死亡率が高く，現在では肝移植はその治療手段として確立していると思われる。本疾患に対する肝移植適応を検討する際には日本急性肝不全研究会基準（**表3**）の他，種々の基準が用いられている。脳症IV度およびV度の症例における神経障害の可逆性については判断が困難であり，術後に昏睡状態から離脱できないか，あるいは覚醒しても重度の神経障害が残る可能性もある。いずれにしても内科的治療が奏功せず脳症が進展する場合は積極的に肝移植の適応を検討することが望ましい。

D．肝細胞癌に対する移植適応

1996年にミラノ基準（遠隔転移と血管侵襲がないもので3 cm，3個以下あるいは5 cm以下の単発肝癌を適応とする）が提唱され，この基

準内における4年生存率は75%と報告された[10]。さらに2001年にミラノ基準を拡大したUCSF基準が発表され，ミラノ基準内と同等の成績が得られるとされている[11]。またわが国の代表的施設でもそれぞれ独自の基準を提唱し，ミラノ基準を逸脱する症例に対して移植適応拡大を試みている[12][13]。肝細胞癌患者の肝機能と腫瘍因子を0から5まで層別化したJISスコアがあり，各スコアにおける従来の治療法による5年生存率を移植成績と比較することで移植適応判定の参考にされることがある[14]。現在，わが国の保険適応はミラノ基準をみたす症例に限定されているが，ミラノ基準を逸脱する症例の中にも予後良好な例が存在するため，今後保険適応基準が再検討される可能性がある。肝機能良好なChild AまたはBにおける肝細胞癌に対する移植適応時期については現在のところ一定の見解はないが，生体肝移植が主体である本邦ではまず肝局所治療を行い，その後の再発症例に対して肝移植を行うsalvage transplantationが提唱されている[15]。移植前治療が3回を超えると再発率が高くなるという報告もあり[16]，再発に対して移植以外の治療を続けるうちに移植適応外の状態に陥ったり，移植後再発リスクを高める状態にならないよう注意が必要である。

III. 生体ドナーの選択からリスクまで

A．ドナー候補者の条件

健常成人の自発的意志に基づく臓器提供が大前提であり，また提供に伴う精神的および身体的リスク（合併症と標準的術後経過など）や社会的リスク（長期休業に対する職場の理解など）についても十分に説明を受け，理解していることが必要である。日本移植学会倫理指針（2007年11月改訂）によれば，『ドナーはレシピエントの親族に限定し，親族は六親等以内の血族と三親等以内の姻族と定義する』とされており，また『有償提供の回避策・任意性の担保に留意する』となっている。現在，成人症例の増加に伴い若年者がドナーとなる頻度が増えているが，周囲からの重圧によって，本当は提供の意思がない場合であっても本心を告知できなかったり，リスクについての理解が不十分であることもあり得るので注意を要する。そこで精神科的診察を含めてドナー候補本人の精神医学的異常の有無だけでなくドナー選択プロセスが適正か否かも判断する。

B．ドナー評価項目

一般的な心電図・呼吸機能検査・胸腹部X線写真・末梢血および生化学検査に加えて，感染症（HBV，HCV，梅毒，ATL，HIV，EBV，CMV）のチェックも行う。HCV，梅毒，ATL，HIV感染者は原則としてドナーにはなれない。耐糖能についてはHbA1cや空腹時血糖で確認する。また非アルコール性脂肪性肝炎（NASH）のスクリーニングとしてHOMA-IRが用いられる他[17]，超音波検査やCT検査で脂肪肝のチェックを行う。脂肪肝が認められたケースでは食事運動療法を数週間から1カ月間程度試みてから最終的に脂肪肝の程度を確認する。多くの施設では上限を30%に設定している。さらにホモ接合型のHLAドナーを除外して移植後GVHDを防ぐ目的でHLAタイピングも行う[18]。

肝臓内外の血管解剖評価を行うとともに腹腔内の異常所見の有無を腹部ダイナミックCT検査でチェックする。さらにMRCPやDIC-CTで胆管解剖を把握する。成人肝移植症例では残肝不足による肝不全の観点からドナーの安全性が問題となることがあるため，残肝容積の割合や移植肝容積（Graft Volume：GV）をCT画像を基に算出する。身長・体重から計算したレシピエントの標準肝容積（Standard Liver Volume：SLV）に対する比率（GV/SLV）が40%以上[19][20]，またはレシピエントの体重に対する比率（Graft Recipient Weight Ratio：GRWR）で0.8%以上あることが望ましい[21]。またドナーの残肝容積の比率は全肝の30～35%以上あることが安全性確保の点から不可欠であり，最低限必要な残肝容積を確保できない場合は，ドナーとして不適格と判断される。

近年PSCの患者に対する血縁ドナーで，術前精査で異常を認めなかったが術中肝生検により初期のPSCがみつかり，手術が中断されたケースが報告され[22]，同疾患の血縁ドナーに対して当院では術前肝生検により組織学的確認を行うことにしている。

C．生体ドナーの術中および術後経過と合併症

生体肝移植におけるドナー手術はレシピエントの手術と同時進行で行われる。移植肝の冷保存時間をできる限り短くするため，レシピエント手術の進行状況に合わせてグラフト摘出のタイミングを図ることもある。当院では左葉グラフト以上の症例において，ドナー手術中の大量出血に備え自己血採取を行っている。多くのドナーは1〜3週間の術後経過で軽快退院し，外来通院に切り替えることが可能である。しかし国内の報告によると約12%の生体肝移植ドナーに術後合併症が発生し，なかでも頻度の高いものは胆汁漏や胆管狭窄などの胆道合併症・胃通過障害・創感染であり[23]，入院治療期間延長の原因となっている。さらに国内で術後肝不全を契機とした生体肝移植ドナー死亡例が報告されている他[24]，海外からも生体ドナーの死亡例や術後肝不全で脳死肝移植を受けた例が報告されており[25]，絶対に回避されなければならない大きな問題である。また生体肝移植ドナーに対する国内の横断的調査では回答者の38.9%が将来の健康への不安を感じており[26]，自験例でもドナーの身体的QOLは術後1年経過しても術前状態まで回復していない可能性があり[27]，ドナー術後長期の身体的側面だけでなく精神面への配慮も非常に重要である。

IV．レシピエント術後管理の注意点

A．免疫抑制療法

肝臓移植後は拒絶反応を抑えるための免疫抑制剤が必要となる。肝移植領域における免疫抑制剤は，tacrolimus（FK506）あるいはcyclosporine（CyA）とステロイド（prednisoloneまたはmethylprednisolone）の2剤を基本とし，場合によってazathioprine（AZA）やmycophenolate mofetil（MMF）など他の薬剤を追加することがある。免疫抑制剤の投与量不足では拒絶反応が惹起される一方で，過量投与は種々の病原体による感染症や腎障害などの副作用を起こし得るため，基本となるFK506やCyAは血中濃度をモニタリングしながら管理する必要があるが，胆汁排泄・消化管吸収・肝機能・感染症など種々の因子に影響を受けるために，目標濃度を得るための投与必要量は症例によって異なる。

急性拒絶反応は30〜40%の症例に認められ，術後1週間から1カ月の間に起こりやすい。まれに発熱・肝脾腫・腹部膨満感・掻痒感などの非特異的な症状を認めることもあるが，多くは血液生化学検査でAST，ALT，γGTP，ALP，ビリルビンなどの上昇を契機に拒絶反応を疑い，肝生検で診断する。治療としては基本的免疫抑制剤の増量とmethylprednisoloneの大量投与を行い，奏功することが多い。

B．感染症対策

免疫抑制療法下では各種感染症のリスクが高まる。術後6週間までは細菌感染が多くみられ，カテーテル感染や腹腔内感染あるいは肺炎などを併発しやすい。MRSAやVREなどの耐性菌に感染する可能性もあり注意を要する[28]。ウイルス感染症は術後1カ月頃からみられ，CMV感染症が多いが，特にCMV抗体陰性のレシピエントの場合は移植後にCMVに感染すると重症化しやすいため，CMVアンチゲネミア法などで早期発見に努める。治療は免疫抑制剤の減量・ganciclovir投与の他，高CMV抗体価グロブリン投与を行うこともある。またEBVの感染では移植後リンパ増殖性疾患（PTLD）を伴うこともあり，特にEBV初感染例は過剰な免疫抑制に注意する。他に合併頻度の高いものに真菌症があるが，術後早期よりβ-Dグルカンを定期的に測定してスクリーニングする。しかしクリプトコッカスなど陽性率が極めて低いものもあるため，臨床的に強く疑われる場合は血清抗原検査やPCR検査を併用し

て結果が出る前に抗真菌剤の投与を開始することもある。

C．早期血管合併症

術後早期は移植肝が凝固能優位状態になっているために肝動脈血栓症のリスクが高まり，施設によってはヘパリン・プロスタグランジンなどで抗凝固療法を行うこともある[29]。またアンチトロンビンIIIも70～80%を目安に維持するよう適宜補充する。肝動脈血栓症および門脈血栓症は急激な肝壊死・肝外胆管壊死を引き起こし得るため早期発見が重要であり，ドップラーエコー検査にて定期的に肝内血流を評価する。血流低下や途絶を認めた場合は造影CTを施行して血管造影による血栓溶解または血行再建術の必要性を判断する[30]。左葉系グラフトでは移植肝の右横隔膜下への落ち込みにより，門脈・肝静脈の捻れが生じることがあるので，術中に移植肝を適切な位置に固定することが肝要である。

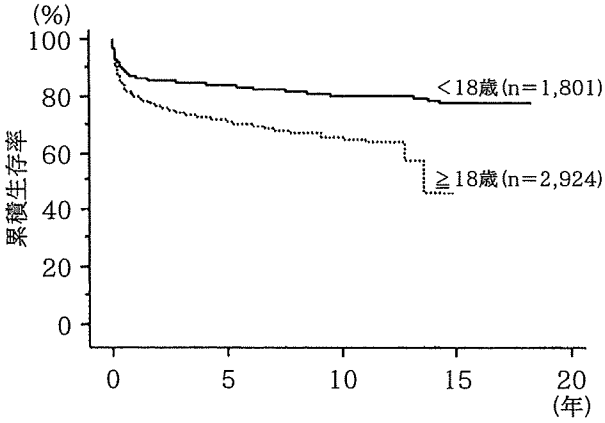

図3　成人と小児の累積生存率
（日本肝移植研究会）

V．生体肝移植の長期成績[3]

2007年末までの症例を対象とした日本肝移植研究会の報告によると，初回移植の場合の1年・3年および5年生存率はそれぞれ83.4%，79.2%，77.0%である。また小児と成人で比較すると，小児のほうがやや良好である（図3）。疾患群で比較すると，血管性疾患・代謝性疾患・胆汁うっ滞性疾患に比べて肝細胞性疾患や腫瘍性疾患は各2群間の比較で有意に予後が悪く，C型肝硬変や肝細胞癌の再発による生存率の低下が影響していると考えられる（図4）。血液型適合性からみた5年生存率は，一致・適合については70%後半で差がないのに対し，不適合では66.2%と低い。

VI．現在の問題点と今後の展望

A．グラフトサイズミスマッチ

Small-for-size graft syndromeの病因は過剰な門脈血流による肝障害やグラフト機能容積の絶対的不足などが考えられており，その対策として脾摘術・脾動脈結紮術や門脈下大静脈シャント作成による門脈血流制御が試みられている[31]。一方，小児症例においては逆にグラフト

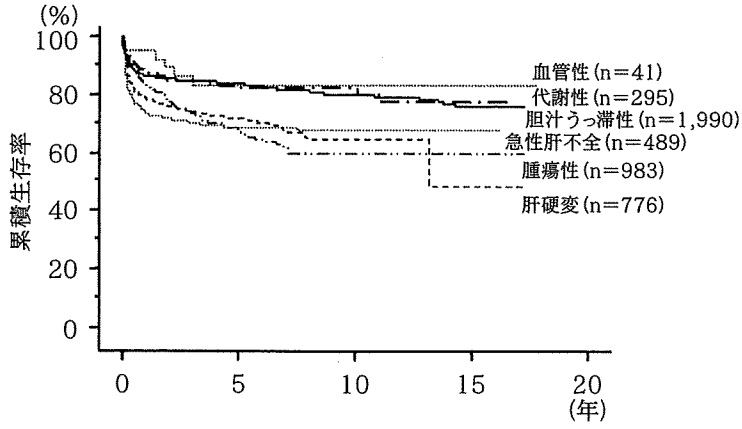

図4　原疾患群別の累積生存率
（日本肝移植研究会）

が大きすぎて流入血流の相対的不足による移植肝壊死が問題になることがあり，GRWRが5%を超える症例ではグラフトの生着率が低く，急性拒絶や門脈血栓が有意に増加するとされている[21]。その対策として，S_2もしくはS_3の単一セグメントを使用することで良好な結果が得られている[32]。

B．ABO血液型不適合肝移植

限られた親族がドナーとなる生体肝移植ではABO血液型不適合の問題は避けられない。血液型不適合移植における液性拒絶反応では，補体活性化・血小板凝集・微小血栓形成が起こり，グラフト内は局所的DICの状態となる。術後1カ月以内に急激な肝壊死を認め，さらに2～3カ月以降に難治性の胆管障害を併発し，術後経過は極めて不良であり，1990年から2000年までの解析では16歳以上の患者の1年および5年生存率は22%と極めて低い[33]。現在では抗ドナー血液型抗体価を低下させるための術前血漿交換に加え，肝局所療法としてステロイド・プロスタグランジンE1などを門脈内注入する方法が2000年に導入され[34]，そして2001年には門脈内に加えて肝動脈内にも持続注入する方法が，2003年には肝動脈のみに注入する方法が導入された。さらに2004年には抗体産生抑制を目的にB細胞表面抗原CD20に対するモノクローナル抗体リツキシマブの術前投与が導入されるようになり，飛躍的に成績が向上した[35]。

C．原疾患の再発

移植後にはウイルス性肝炎・自己免疫疾患・肝細胞癌などの原疾患再発を認めることがある。

ウイルス性肝炎ではB型肝炎再発が以前より問題であったが，B型肝炎免疫グロブリン(HBIG)およびラミブジン（逆転写酵素阻害剤）が再発予防に使用されるようになり[36]，現在では移植後1～2年における再感染率は10%未満とされているものの[37]，ラミブジン耐性変異株の出現とHBIGの長期使用に伴う医療費高騰が問題となっている。一方C型肝炎ウイルスの再感染はほぼ全例で認められ，治療を行わない場合は移植後5年以内に20～40%が肝硬変に進行するとされる。またfibrosing cholestatic hepatitisといわれる重篤な急性肝炎を発症する症例もあり，重要な問題となっている[38][39]。現在，移植後再発C型肝炎に対する標準的治療はペグインターフェロンとリバビリンの併用療法である。

PBCでは抗ミトコンドリア抗体陽性が特徴的ではあるが，移植後も引き続き陽性のままであり，再発の指標とはならない。再発の確定診断には組織学的にPBCに特徴的な像が証明されることが必要である[40]。PBCではHLAの一致しているドナーからの移植症例で再発が多く認められており，血縁間の生体肝移植は再発のリスクとなる可能性が示唆されている[41]。またPSCの移植患者で後に肝内外胆管に狭窄を認め，加えて硬化性胆管炎様の病理所見がある場合はPSC再発と診断し得る[42]。この他，自己免疫性肝炎（AIH）も同様に移植後再発することがあるが，その診断は難しく初期の組織像は急性拒絶反応に酷似している場合もある。また原疾患が自己免疫性肝疾患でない移植症例の一部に，AIHと類似した移植肝障害を認めた例が報告され，AIHと同様の治療が有効であったために*de novo* AIHと呼ばれるようになった[43]。

肝細胞癌に対する移植後の再発の危険因子として腫瘍サイズ・脈管浸潤・低分化組織型などが指摘されている。術前針生検の必要性が考慮されているが，出血やneedle track implantationの危険性などその施行には多くの問題点が指摘されている。

D．マージナルグラフト

脳死肝移植が進展しない状況の中で，生体ドナーの限界を安全に拡大させる必要性が指摘されている。脂肪沈着がグラフトとして不適切とされる根拠は，冷保存期間中に癒合拡大した脂肪によって肝細胞や類洞を圧迫して血流障害が生じたとする脳死肝移植の経験に基づいている。しかし生体肝移植においては脳死肝移植に比べて冷保存期間が短いため，ある程度の脂肪肝は許容される可能性もある。実際に，20～

50%までの脂肪肝であれば生体肝移植が可能とする報告もある[44]。

現在，多くの施設がドナーの年齢上限を60～65歳に設定している。加齢に基づくドナー自身の危険性以外に移植肝の予備能低下の可能性も無視できず，移植肝が小さいケースでは特に注意が必要である。

E．免疫抑制剤からの離脱

免疫抑制剤に関しては，ステロイドの早期離脱はほぼ可能となったが，カルシニューリン阻害剤の減量または完全離脱が今後の目標である。EBウイルス感染症やPTLDなどの理由から免疫抑制剤を中止した後も拒絶反応が起きない例があることがわかり，ある一定の基準を満たす症例に限定して免疫抑制剤離脱の試みが行われている施設もある[45]。

おわりに

生体肝移植の歴史と現状，現在の具体的な問題点について概説した。わが国では脳死肝移植が発展せず，生体肝移植の役割がさらに重要となってきているが，現在肝移植を必要とする患者の中で実際に移植を受けているのはわずかに2割程度と思われる。今後，ウイルス性肝硬変や肝細胞癌などの症例が増加し，ドナー不足はますます深刻化するものと予想される。ドナープールの拡大の必要性もさることながら，生体肝移植においては生体ドナーの安全性が最優先事項であり，重篤な合併症は絶対に避けられねばならないので適応拡大は慎重に検討されるべきである。今後の生体肝移植の成績向上および問題点の解決に対して努力するとともに，脳死ドナーの増加を期待したい。

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Original article

Mild hepatic macrovesicular steatosis may be a risk factor for hyperbilirubinaemia in living liver donors following right hepatectomy

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Background: The aim of this study was to evaluate the effects of mild macrovesicular steatosis on the outcome of living liver donors following right hepatectomy.
Methods: The medical records of 46 living liver donors who underwent right hepatectomy were studied. Ten donors had mild macrovesicular steatosis (5–10 per cent in seven and 11–20 per cent in three patients). Five donors with other liver pathology were excluded. Outcome in these ten donors (group 1) was compared with that in the remaining 31 donors with normal liver histology (group 2).
Results: The median duration until normalization of total bilirubin levels was 14 and 5 days in groups 1 and 2 respectively ($P = 0{\cdot}028$). The peak total bilirubin level was significantly higher in group 1 than in group 2 (80·4 *versus* 49·6 μmol/l; $P = 0{\cdot}033$). Multivariable analysis showed mild macrovesicular steatosis to be an independent risk factor for hyperbilirubinaemia (odds ratio 7·94 (95 per cent confidence interval 1·17 to 54·03); $P = 0{\cdot}034$).
Conclusion: Mild macrovesicular steatosis may be related to adverse outcome in living liver donors who undergo right hepatectomy and, in terms of donor safety, is of potential concern in donor selection.

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Introduction

In Japan, living donor liver transplantation (LDLT) accounts for 99 per cent of all liver transplantation procedures. Only 45 deceased donor liver transplants have been performed over the past 10 years, as religious, emotional and historical issues present long-standing obstacles to this form of transplantation. In cases of deceased donor transplantation, the use of marginal donors, such as those with moderate steatosis, to increase the donor pool has been discussed worldwide. With LDLT it is important to consider the condition of both recipient and donor, because donor safety is of the highest priority[1–4]. Macrovesicular steatosis is an independent predictor of complications following hepatic resection[5–12].

In terms of graft quality, severe macrovesicular steatosis greater than 60 per cent is often associated with primary non-function, resulting in serious sequelae for liver transplant recipients[11,13,14]. In addition, the acceptable level of steatosis in LDLT is thought to be lower than that in deceased donor liver transplantation, because of the smaller sized graft[15–17]. Macrovesicular steatosis can also lead to inflammation and fibrosis, and recipients of a liver graft with macrovesicular steatosis are potentially more susceptible to graft damage, such as preservation injury and acute cellular rejection[10,14]. To ensure recipient safety, most centres use liver grafts with up to 30 per cent macrovesicular steatosis[11,17–20].

In terms of donor safety, it is generally accepted that moderate or severe macrovesicular steatosis should be avoided, to prevent complications in the donor[7,12,17,19,21]. Kim and colleagues[22] reported that right hepatectomy could be performed safely for the donor when the liver had macrovesicular steatosis of less than 10 per cent. However, the actual risk of mild macrovesicular steatosis (less than

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20 per cent steatosis) in living liver donors remains to be elucidated and, particularly in right hepatectomy, the risks should not be underestimated.

The purpose of this study was to evaluate the safety of donors with mild macrovesicular steatosis following right hepatectomy in terms of functional hepatic recovery, as well as perioperative complications and remnant liver regeneration. In addition, the relationships between preoperative factors, such as laboratory data and imaging results, and mild macrovesicular steatosis were evaluated.

Methods

Between January 2003 and April 2007, 76 LDLT procedures were performed at Nagoya University Hospital. After excluding 30 donors who underwent an extended right hepatectomy (right liver graft with middle hepatic vein), left hepatectomy (left liver graft) or left lobectomy (left lateral segment graft), 46 living liver donors (32 men and 14 women) who underwent a standard right hepatectomy (right liver graft without middle hepatic vein) were evaluated. All subjects were approved as donor candidates after evaluation of their general physical condition as well as psychosocial assessments.

Preoperative evaluation

Routine preoperative examinations were conducted including blood tests, urinalysis, electrocardiography, spirography, plain chest and abdominal radiological studies, ultrasonography and multidetector row computed tomography (CT). The liver-to-spleen CT attenuation values ratio (L/S ratio = mean attenuation value for the liver (16 points, four in each segment of the right hemiliver)/mean attenuation value for the spleen (four points)) was calculated for all donors as a parameter of macrovesicular steatosis.

Estimated total liver, graft liver and remnant liver volume were calculated using CT volumetry analysis. The acceptable graft-to-recipient weight ratio and remnant liver volume ratio (RLVR) were set at greater than 0·8 and 35 per cent respectively (graft-to-recipient weight ratio (%) = estimated graft volume (ml)/recipient bodyweight (g) × 100; RLVR (%) = (estimated whole liver volume (ml) − estimated graft liver volume (ml)) × 100/estimated whole liver volume (ml)). Seven donors with a RLVR lower than 35 per cent were accepted after comprehensive evaluations.

Surgical procedure

After identification of the hepatic artery and portal vein(s), the right lobe was mobilized from the inferior vena cava, and the right hepatic vein was defined and encircled. Before dissecting the liver, cholangiography was performed to clarify the biliary anatomy. A Cavitron ultrasonic surgical aspirator (CUSA®; Valleylab, Boulder, Colorado, USA) and bipolar coagulation were used to transect the liver parenchyma at the right side of the middle hepatic vein. Some 3 min after heparin administration (1000 units), the right hepatic artery, right portal vein(s) and hepatic veins were clamped and divided. The graft was flushed with cold University of Wisconsin solution (Viaspan®; Dupont, Wilmington, Delaware, USA).

Histopathological evaluation

At the start of the hepatic resection, a liver biopsy was taken from segment IV (time zero biopsy). Two pathologists, experienced in the analysis of living liver donors as well as liver recipients, evaluated each specimen for steatosis, fibrosis and other pathology. Ten of the donors had mild macrovesicular steatosis (5–10 per cent, seven donors; 11–20 per cent, three donors) (group 1). Two of these ten donors also had mild microvesicular steatosis of less than 10 per cent. Microvesicular steatosis was not included in this analysis, because it does not appear to influence postoperative liver function; thus, it has less impact on residual liver function and regeneration in the donor. There was no other liver pathology in the other eight donors. Two donors had mild portal fibrosis, two had mild lobular hepatitis of unknown aetiology, and one had some focal pericentral necrosis. Although these five donors (three men and two women) had no known history of liver disease and their preoperative liver function test results were within normal limits, they were excluded from the analysis. In the remaining 31 donors (group 2), histopathological findings for time zero biopsies were normal.

Postoperative evaluation

Liver function test results, including total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and γ-glutamyl transferase (GGT) values, were compared between groups 1 and 2. Blood tests were performed routinely on postoperative days 1, 2, 3, 5, 7, 10, 14 and 21, and 1, 2, 3, 6 and 12 months after surgery. From January 2005, remnant liver regeneration was determined in all donors by CT volumetry analysis at 2 weeks, and 1, 3, 6 and 12 months after surgery. Regeneration was estimated

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by calculating the ratio of the actual liver volume at this time point to the original liver volume before resection.

Postoperative complications were evaluated based on a modified Clavien grading system[23]: grade I, deviation from normal postoperative course without need for therapy; grade II, complication requiring pharmacological treatment; grade III, complication requiring surgical, endoscopic or radiological intervention (IIIa/b: without/with general anaesthesia); grade IV, life-threatening complication requiring intensive care; grade V, death. In the evaluation of complications, infection was diagnosed from microbiological analysis, laboratory data and/or imaging studies, as well as clinical symptoms. Autologous transfusion was considered a complication, because it was performed only when there was excessive intraoperative blood loss.

Evaluation of impact of mild macrovesicular steatosis in living liver donors

The value of preoperative laboratory data, body mass index (BMI) and L/S ratio as screening factors for macrovesicular steatosis in living liver donors was assessed. In addition, the effect of mild macrovesicular steatosis on the postoperative course was evaluated in terms of recovery of liver function, postoperative complications and remnant liver regeneration after right hepatectomy.

Statistical analysis

Values are presented as median (range). Comparison analysis was performed by non-parametric methods, using the Mann–Whitney *U* test for continuous variables and χ^2 tests for categorical variables. A logistic regression model was used in analyses for detecting risk factors. Differences were considered statistically significant when $P < 0{\cdot}050$. SPSS® version 15·0J (SPSS, Chicago, Illinois, USA) was used for statistical analysis.

Results

Preoperative donor evaluations

Receiver–operator characteristic (ROC) curves for BMI, L/S ratio, preoperative ALT and preoperative GGT were determined to compare the ability of these factors to discriminate between normal livers and livers with mild macrovesicular steatosis (*Fig. 1*). For BMI and L/S ratio, the differences between the groups were not statistically significant (*Table 1*), and the ROC curves indicated that these variables would not be of value in predicting the presence of mild macrovesicular steatosis in living liver donors. On the other hand, median preoperative ALT and GGT levels were significantly higher in group 1 than in group 2 (*Table 1*). In addition, the ROC curves for ALT and GGT were closer to the upper left corner than those for BMI and L/S ratio (*Fig. 1*), indicating better sensitivity and specificity.

Operative details and hospital stay

There were no significant differences between the groups in terms of surgical procedures, such as operating time and

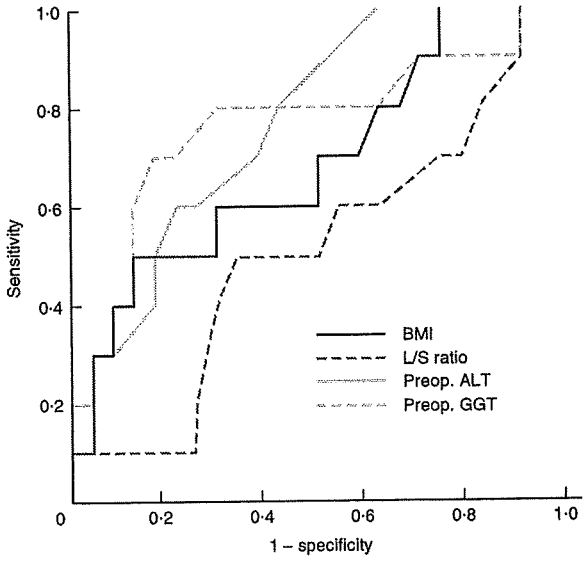

Fig. 1 Receiver–operator characteristic curves for body mass index (BMI), liver-to-spleen computed tomography attenuation values ratio (L/S ratio) and liver function tests used to detect mild macrovesicular steatosis. ALT, alanine aminotransferase; GGT, γ-glutamyl transferase

Table 1 Patient demographics

	Group 1 ($n = 10$)	Group 2 ($n = 31$)	*P*
Age (years)*	42 (21–56)	35 (20–60)	0·211†
Sex ratio (M : F)	7 : 3	22 : 9	0·633‡
RLVR (%)*	37 (29–45)	39 (33–50)	0·351†
BMI (kg/m^2)*	22·9 (19·4–29·3)	21·4 (17·4–25·6)	0·117†
L/S ratio*	1·26 (1·10–1·42)	1·24 (1·04–1·40)	0·928†
ALT (units/l)*	21 (15–62)	15 (7–42)	0·008†
GGT (units/l)*	28 (11–53)	18 (10–43)	0·014†

*Values are median (range). RLVR, remnant liver volume ratio; BMI, body mass index; L/S ratio, liver-to-spleen computed tomography attenuation values ratio; ALT, alanine aminotransferase; GGT, γ-glutamyl transferase. †Mann–Whitney *U* test; ‡χ^2 test.

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Table 2 Clinical characteristics

	Group 1 ($n = 10$)	Group 2 ($n = 31$)	P†
Operating time (min)*	547 (365–911)	540 (320–901)	0·939
Estimated blood loss (ml)*	210 (108–2800)	582 (70–3448)	0·123
Autologous transfusion	2	5	
Allogeneic transfusion	1	0	
Hospital stay (days)*	20·5 (14–36)	17·5 (10–43)	0·214

*Values are median (range). †Mann–Whitney U test.

estimated blood loss (*Table 2*). Autologous transfusions were required in two donors in group 1 and five in group 2 as a result of excessive blood loss during surgery. Owing to progressive anaemia, one donor in group 1 required allogeneic transfusion on the second postoperative day. Hospital stay was longer than 4 weeks in two donors in group 1 (one intra-abdominal infection and one wound infection, treated by antibiotics and irrigation respectively) and three donors in group 2 (one wound infection, one bile leak and one intractable atelectasis due to right pleural effusion, treated by secondary closure, percutaneous drainage and conservative measures respectively). There was no significant difference between the groups in terms of length of hospital stay. No morbidity related to the presence of mild macrovesicular steatosis causing an extended hospital stay was observed.

Postoperative laboratory data

Median levels of total bilirubin were significantly higher in group 1 on postoperative days 3, 5, 7, 10 and 14 ($P = 0·017$, $P = 0·011$, $P = 0·036$, $P = 0·031$ and $P = 0·006$ respectively), and at 1, 3 and 6 months after surgery ($P = 0·018$, $P = 0·024$ and $P = 0·028$ respectively) (*Fig. 2a*). Median peak levels of total bilirubin indicated that none of the donors had indirect hyperbilirubinaemia; levels in groups 1 and 2 were 80·4 (range 37·6–249·7) and 49·6 (20·5–121·4) μmol/l respectively ($P = 0·033$), and median peak direct bilirubin levels were 34·2 (range 13·7–133·4) and 18·8 (6·8–88·9) μmol/l respectively ($P = 0·031$). The median time to normalization of total bilirubin levels (normal range less than 20·5 μmol/l) was 14 (range

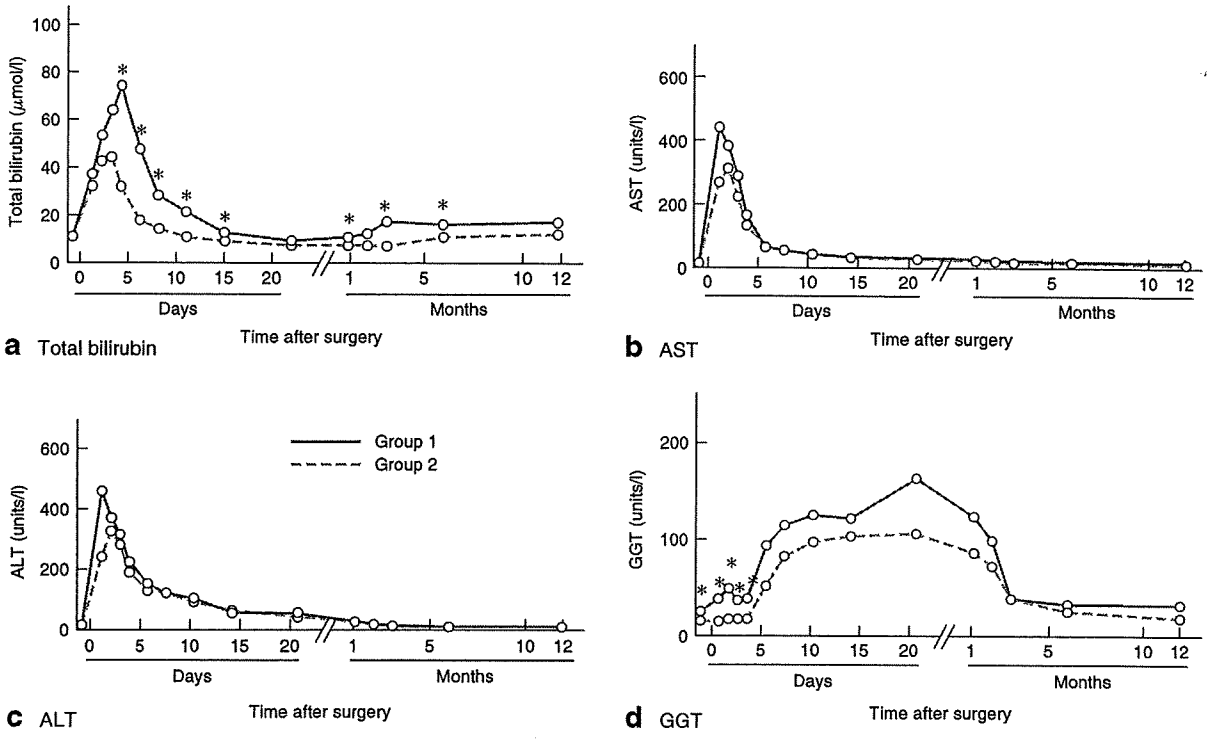

Fig. 2 Changes in median postoperative laboratory values in ten donors with macrovesicular steatosis (group 1) and 31 donors with normal liver histology (group 2). **a** Total bilirubin; **b** aspartate aminotransferase (AST); **c** alanine aminotransferase (ALT); **d** γ-glutamyl transferase (GGT). *$P < 0·050$ *versus* group 2 (Mann–Whitney U test)

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