厚生労働科学研究費補助金　（エイズ対策研究事業）
分担研究報告書
HIV/HCV 重複感染患者の予後調査（中間報告）

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研究要旨　HIV/HCV 重複感染患者の長期予後を知る目的で、2004 年に調査を行った患者 138 名の追跡調査を行った。10 年の追跡期間中に 21 名が死亡しており死亡時年齢の中央値は 50 歳であった。死因は肝硬変（肝不全）６例、肝細胞癌３例、PML３例の順であった。食道静脈瘤の発生を 17 例、非代償性肝硬変への進展を 12 例、肝細胞癌の合併を９例にそれぞれ認めた。これらのいずれかの合併は 27 例に認められた。HIV/HCV 重複感染患者の約２割が 10 年以内に進行肝疾患に進展し、その４割近くが死亡することが判明した。進行肝疾患の合併年齢の中央値は 51 歳であり、HIV 合併により進展速度が早くなることも示唆された。

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A. 研究目的

本邦の HIV/HCV 重複感染例は血友病の患者が多い。若い頃から頻回に輸血を受けていることもあり、HCV への罹患年齢が若く、若年で進展慢性肝疾患に至る可能性がある。HIV への重複感染があることも肝疾患の進展を早める原因である。本研究の目的はこうした症例における肝疾患の進展に関する知見を得ることである。

B. 研究方法

2004 年に“HIV/HCV 重複感染症における肝疾患ガイドライン”を作成する目的で厚生労働省研究班（小池和彦班長）において肝機能の断面調査を行い、2009 年にその追跡調査を行った。本研究では調査に参加した施設のうち、本年１月までに追跡調査の結果が出そろった３施設での予後調査を行った。

（倫理面への配慮）

東京大学医学部倫理委員会に“ヒト免疫不全ウイルス（ＨＩＶ）感染者におけるＣ型肝炎ウイルス感染症の予後因子に関する研究”ということで申請し、研究許可を得ている（審査番号 10678）。

C. 研究結果

３施設から合計 138 例の症例がエントリーされた。以下の点に関して解析を行った。

（１）生命予後

2004 年から 2014 年の間に 138 例中 21 例（15%）が死亡していた。死亡時年齢の中央値は 50 歳であった。死因としては、①肝硬変（肝不全）６例、②　肝細胞癌　３例、②　PML３例、④　腎不全２例、④　多臓器不全２例、⑥悪性リンパ腫、直腸癌、肺炎、乳酸アシドーシス、インターフェロン投与中の原因不明死、各１例であり、肝疾患関連死は９例（43%）であった。

（２）食道静脈瘤の合併

肝硬変、非肝硬変を問わず、門脈圧亢進症の所見として観察される可能性がある。本研究では 17 例（12%）に 10 年以内の食道静脈瘤合併が見られた。発症年齢の中央値は 43 歳であった。17 例中 14 例は 1990 年代に ART が導入されていた。17 例中 11

例は血小板数 100000/uL 未満であり、残りの６例中５例はアルブミン値が４g・dL 未満であり、17 例中 16 例は臨床的に肝硬変が疑われた。

（３）肝不全の合併

腹水または肝性脳症の出現をもって肝不全の合併とした。12 例（９%）にいずれかの出現を見た。発症年齢の中央値は 50 歳であった。12 例中 9 例は肝細胞癌の合併のない症例であった。ビリルビンが 3mg/dL 以上に上昇した症例が 13 例あったが、1 例を除いて肝不全もしくは肝細胞癌の合併例であった。

（４）肝細胞癌の合併

肝細胞癌の合併は９例（６%）に見られ、うち６例は死亡した。平均罹病期間は 3 年であった。発症年齢の中央値は 60 歳。９例中８例は血友病の症例であった。

（５）進展慢性肝疾患の合併

（２）から（４）までの少なくともいずれかを合併する患者は 27 例（19%）であった。年齢の中央値は 51 歳であった。

D. 考察

本邦の HIV/HCV 重複感染例は血友病の患者が多く、肝疾患の進展に関しても諸外国と一律に考えることができない。

今回の調査では肝疾患で亡くなる血友病患者が 10 年間で 6.5%（138 人中 9 名）、即ち年率 0.65%であった。現在血友病者で肝疾患のため毎年数名が亡くなっている状況に合致する数値である。その他日和見感染である PML で亡くなる人が死因として目立った。

食道静脈瘤の合併が 10 年間で 12%に認められた。その 90%近くは肝硬変を伴っている。発症年齢の中央値は 43 歳と若く、長い罹患歴、HIV 治療に用いられた d-drug の影響が考えられた。

肝不全の合併は年率 0,9%程度であった。HCV 単独感染症では肝細胞癌の合併が高頻度に見られるが、今回のコホートでは 75%の症例には肝細胞癌の合併は見られなかった。肝移植の適応になる症例がかなり含まれていることを示唆するデータであった。

肝細胞癌の発症は年率 0.6%であったが、９例中６例が亡くなっており、罹病期間は３年であった。これは HCV 単独感染症と比較して明らかに短く、HIV/HCV 重複感染例における治療の困難さを反映したものと考えられる。

進展慢性肝疾患のイベントは 10 年間で 19%に認められており、今後 DAA 併用療法によるウイルス排除が極めて大切である。

E. 結論

HIV/HCV 重複感染者の半数近くは現座も肝臓病のために亡くなる。イベント発生は 50 歳前後であり、早急な抗ウイルス療法の導入が臨まれる。

F. 健康危険情報

なし

G. 研究発表

１．論文発表

Ohgishi M, Yotsuyanagi H, Tsutsumi T, Gatanaga H, Ode H, Sugiura W, Moriya K, Oka S, Kimura S, Koike K. Deconvoluting the composition of low-frequency hepatitis C viral quasispecies: Comparison of genotypes and NS3 resistance-associated variants between HCV/HIV coinfected hemophiliacs and HCV monoinfected patients in Japan. Plos One [Epub ahead of print]

２．学会発表

大岸誠人、四柳宏ほか。HCV/HIV 重複感染を有する血友病患者における多重 Genotype 感染歴・NS3 プロテアーゼ阻害剤に対する自然耐性変異の頻度に関する検討。第２８回日本エイズ学会学術集会・総会　大阪市

H. 知的財産権の出願・登録状況（予定を含む。）

１．特許取得

該当なし

２．実用新案登録

該当なし

３．その他

該当なし

III. 研究成果の刊行に関する一覧表

別紙４

研究成果の刊行に関する一覧表

書籍：

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
Genda T, Ichida T.	Liver Transplantation for primary biliary cirrhosis.	Ohira H	Autoimmune Liver Disease.	Springer *0.*	Tokyo	2014	287-30
田浦直太, 市川辰樹, 中尾一彦	高齢者肝癌症例の特徴と予後についての検討		消化器内科	科学評論社	東京	2014	72-76
田浦直太, 加藤有史, 市川辰樹, 中尾一彦	住民検診による T 地区における HBs 抗原消失についての検討		消化器内科	科学評論社	東京	2014	203-206
四柳宏	主要な感染症 肝炎ウイルス感染症	河野茂 跡見裕	感染症診療 update	日本医師会			400 - 401
四柳宏	HIV と肝炎ウイルスとの重複感染症	満屋裕明	HIV 感染症と AIDS	最新医学社			91 - 99

雑誌：

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Hara T, Soyama A, Takatsuki M, Hidaka M, Carpenter I, Kinoshita A, Adachi T, Kitasato A, Kuroki T, Eguchi S.	The Impact of Treated Bacterial Infections within One Month before Living Donor Liver Transplantation in Adults.	Ann Transplant.	19	674-9	2014
Baimakhanov Z, Soyama A, Takatsuki M, Hidaka M, Hirayama T, Kinoshita A, Natsuda K, Kuroki T, Eguchi S.	Preoperative simulation with 3D printed solid model for one-step reconstruction of multiple hepatic veins during living donor liver transplantation.	Liver Transpl.	21(2)	266-8	2015
Takatsuki M, Soyama A, Hidaka M, Kinoshita A, Adachi T, Kitasato A,	Prospective study of the safety and efficacy of intermittent inflow occlusion (Pringle	Hepatol Res.	-	-	2014 [Epub ahead

Kuroki T, Eguchi S.	maneuver) in living donor left hepatectomy.				of print]
Hirabaru M, Mochizuki K, Takatsuki M, Soyama A, Kosaka T, Kuroki T, Shimokawa I, Eguchi S.	Expression of alpha smooth muscle actin in living donor liver transplant recipients.	World J Gastroenterol.	20(22)	7067-74	2014
Eguchi S, Soyama A, Takatsuki M, Hidaka M, Adachi T, Kitasato A, Baimakhanov Z, Kuroki T.	How to explant a diseased liver for living donor liver transplantation after previous gastrectomy with severe adhesion (with video).	J Hepatobiliary Pancreat Sci.	21(8)	E62-4	2014
Takatsuki M, Baimakhanov Z, Soyama A, Inoue Y, Hidaka M, Kuroki T, Eguchi S.	Obstructing spontaneous major shunt vessels might not be mandatory to maintain adequate portal inflow in living donor liver transplantation.	Transplantation.	97(9)	E52-3	2014
Takatsuki M, Soyama A, Muraoka I, Hara T, Kinoshita A, Yamaguchi I, Tanaka T, Kuroki T, Eguchi S.	Post-operative complications requiring hospitalization more than one yr after living donor liver transplantation.	Clin Transplant.	28(1)	105-10	2014
Eguchi S, Takatsuki M, Kuroki T.	Liver transplantation for patients with human immunodeficiency virus and hepatitis C virus co-infection: update in 2013.	J Hepatobiliary Pancreat Sci.	21(4)	263-8	2014
Soyama A, Takatsuki M, Adachi T, Kitasato A, Torashima Y, Natsuda K, Tanaka T, Yamaguchi I, Tanaka S, Kinoshita A, Kuroki T, Eguchi S.	A hybrid method of laparoscopic-assisted open liver resection through a short upper midline laparotomy can be applied for all types of hepatectomies.	Surg Endosc.	28(1)	203-11	2014
Tanaka T, Takatsuki M, Hidaka M, Hara T, Muraoka I, Soyama A, Adachi T, Kuroki T, Eguchi S.	Is a fluorescence navigation system with indocyanine green effective enough to detect liver malignancies?	J Hepatobiliary Pancreat Sci.	21(3)	199-204	2014
Takatsuki M, Soyama A, Eguchi S.	Liver transplantation for HIV/hepatitis C virus co-infected patients.	Hepatol Res.	44(1)	17-21	2014
夏田孔史、曽山明彦、高槻光寿、山口東平、虎島泰洋、北里周、足立智彦、	HIV/HCV 重複感染患者の肝障害病期診断における acoustic radiation force impulce (ARFI)	日本消化器病学会雑誌	111(4)	737-742	2014

黒木保、市川辰樹、中尾一彦、江口晋	elastography の有用性.				
Ogawa Y, Watanabe D, Hirota K, Ikuma M, Yajima K, Kasai D, Mori K, Ota Y, Nishida Y, Uehira T, Mano M, Yamane T, Shirasaka T	Rapid Multiorgan Failure due to Large B-cell Lymphoma Arising in Human Herpesvirus-8-associated Multicentric Castleman's Disease in a Patient with Human Immunodeficiency Virus Infection	Intern Med.	53(24)	2805-9	2014
Yajima K, Uehira T, Otera H, Koizumi Y, Watanabe D, Kodama Y, Kuzushita N, Nishida Y, Mita E, Mano M, Shirasaka T	A case of non-cirrhotic portal hypertension associated with anti-retroviral therapy in a Japanese patient with human immunodeficiency virus infection	J Infect Chemother	20(9)	582-5	2014
Ohnishi K, Sakamoto N, Kobayashi K, Iwabuchi S, Nakamura-Uchiyama F, Ajisawa A, Yamauchi Y, Takeshita N, Yamamoto Y, Tsunoda T, Yoshimura Y, Tachikawa N, Uehira T	Subjective adverse reactions to metronidazole in patients with amebiasis	Parasitol Int.	63(5)	698-700	2014
Katano H, Hishima T, Mochizuki M, Kodama Y, Oyaizu N, Ota Y, Mine S, Igari T, Ajisawa A, Teruya K, Tanuma J, Kikuchi Y, Uehira T, Shirasaka T, Koibuchi T, Iwamoto A, Oka S, Hasegawa H, Okada S, Yasuoka A	The prevalence of opportunistic infections and malignancies in autopsied patients with human immunodeficiency virus infection in Japan	BMC Infect Dis.	14	229	2014
Kojima Y, Hagiwara S, Uehira T, Ajisawa A, Kitanaka A, Tanuma J, Okada S, Nagai H	Clinical outcomes of AIDS-related Burkitt lymphoma: a multi-institution retrospective survey in Japan	Jpn J Clin Oncol.	44(4)	318-23	2014
Ota Y, Hishima T, Mochizuki M, Kodama Y, Moritani S, Oyaizu N, Mine S, Ajisawa A, Tanuma J, Uehira T,	Classification of AIDS-related lymphoma cases between 1987 and 2012 in Japan based on the WHO classification of lymphomas, 4th edition.	Cancer Med.	3(1)	143-53	2014

Hagiwara S, Yajima K, Koizumi Y, Shirasaka T, Kojima Y, Nagai H, Yokomaku Y, Shiozawa Y, Koibuchi T, Iwamoto A, Oka S, Hasegawa H, Okada S, Katano H					
上平朝子、西田恭治	連載 エイズに見られる感染症と悪性腫瘍（１４）進行性多巣性白質脳症	化学療法の領域	30(12)	2152-9	2014
杉本彩, 中水流正一, 山田拓哉, 上平朝子, 細見尚弘, 三田英治	急性膵炎に伴う脾動脈瘤に対してコイル塞栓術を施行したHIV感染者の１例	膵臓	29(3)	673	2014
杉本彩, 中水流正一, 福富啓祐, 日比野賢嗣, 木村圭一, 田村猛, 坂根貞嗣, 岩崎哲也, 岩崎竜一朗, 長谷川裕子, 榊原祐子, 山田拓哉, 外山隆, 石田永, 小川吉彦, 矢嶋敬史郎, 上平朝子, 児玉良典, 三田英治	肝生検で診断されたAIDS関連バーキットリンパ腫の２例	日本消化器病学会雑誌	111(suppl-1)	429	2014
杉本彩, 山田拓哉, 福富啓祐, 木村圭一, 日比野賢嗣, 岩崎哲也, 岩崎竜一朗, 長谷川裕子, 榊原祐子, 中水流正一, 石田永, 上平朝子, 森清, 三田英治	HIV感染者に発症した消化管カポジ肉腫に対する肉眼型診断と病理組織診断との検討	日本消化器病学会雑誌	111(suppl-2)	973	2014
大熊裕介, 田沼順子, 大寺博, 小島勇貴, 四本美保子, 竹田雄一郎, 上平朝子, 永井宏和, 味澤篤, 瀬戸口靖弘, 岡田誠治	本邦のエイズ基幹病院におけるHIV感染者に合併した肺がんの多施設調査	肺癌	54(5)	340	2014
吉岡巌, 金宮健翁, 木下竜弥, 鄭則秀, 原田泰規, 上平朝子, 白阪琢磨, 岡聖次	抗HIV薬Atazanavir内服患者に発生した尿路結石症の検討	泌尿器外科	27(11)	1823-7	2014
Genda T, Ichida T, Sakisaka S, Sata M, Tanaka E, Inui A, Egawa H, Umeshita K, Furukawa H, Kawasaki S, Inomata Y.	Waiting list mortality of patients with primary biliary cirrhosis in the Japanese transplant allocation system.	J Gastroenterol	49	324-331	2014

Narita Y, Genda T, Tsuzura H, Sato S, Kanemitsu Y, Ishikawa S, Kikuchi T, Hirano K, Iijima K, Wada R, Ichida T.	Prediction of liver stiffness hepatocellular carcinoma in chronic hepatitis C patients on interferon-based anti-viral therapy.	J Gastroenterol Hepatol.	29	137-143	2014
Tsuzura H, Genda T, Sato S, Murata A, Kanemitsu Y, Narita Y, Ishikawa S, Kikuchi T, Mori M, Hirano K, Iijima K, Wada R, Ichida T.	Expression of aldo-keto reductase family 1 member B10 in the early stages of human hepatocarcinogenesis.	Int J Mol Sci.	15	6556-68	2014
Akamatsu N, Sugawara Y, Kokudo N.	Living-donor vs deceased-donor liver transplantation for patients with hepatocellular carcinoma.	World J Hepatol.	27;6(9)	626-31	2014
Harada N, Tamura S, Sugawara Y, Togashi J, Ishizawa T, Kaneko J, Aoki T, Sakamoto Y, Hasegawa K, Tanaka T, Yamashiki N, Kokudo N.	Impact of donor and recipient single nucleotide polymorphisms of IL28B rs8099917 in living donor liver transplantation for hepatitis C.	PLoS One.	5;9(3)		2014
Ishikane M, Watanabe K, Tsukada K, et al.	Acute Hepatitis C in HIV-1 Infected Japanese Cohort: Single Center Retrospective Cohort Study.	PLoS One.	19;9(6)		2014
Miyaaki H, Ichikawa T, Taura N, Miuma S, Isomoto H, Nakao K.	Endoscopic management of esophagogastric varices in Japan.	Ann Transl Med	2(5)	42	2014
Senoo T, Ichikawa T, Taura N, Miyaaki H, Miuma S, Shibata H, Honda T, Takatsuki M, Hidaka M, Soyama A, Eguchi S, Nakao K.	Incidence of and risk factors for bile duct stones after living donor liver transplantation: An analysis of 100 patients.	Hepatol Res			2014
Kawaguchi T, Kohjima M, Ichikawa T, Seike M, Ide Y, Mizuta T, Honda K, Nakao K, Nakamuta M, Sata M	The morbidity and associated risk factors of cancer in chronic liver disease patients with diabetes mellitus: a multicenter field survey.	J Gastroenterol			2014
Kamo Y, Ichikawa T, Miyaaki H, Uchida S, Yamaguchi T, Shibata H, Honda T, Taura N,	Significance of miRNA-122 in chronic hepatitis C patients with serotype 1 on interferon therapy.	Hepatol Res			2014

Isomoto H, Takeshima F, Nakao K.					
Nakao K, Miyaaki H, Ichikawa T	Antitumor function of microRNA-122 against hepatocellular carcinoma.	J Gastroenterol	49(4)	589-93	2014
Miyaaki H, Ichikawa T, Kamo Y, Taura N, Honda T, Shibata H, Milazzo M, Fornari F, Gramantieri L, Bolondi L, Nakao K.	Significance of serum and hepatic microRNA-122 levels in patients with non-alcoholic fatty liver disease.	Liver Int	34(7)	e302-7	2014
柴田英貴、北山　素、加茂泰広、本田琢也、三馬聡、宮明寿光、田浦直太、市川辰樹、中尾一彦	精神疾患を有するC型慢性肝炎に対してインターフェロンBによる治療を行った例の検討	肝臓	55(12)	764-766	2014
Marubashi S, Wada H, Kawamoto K, Kobayashi S, Eguchi H, Doki Y, Mori M, Nagano H.	Laparoscopy-assisted hybrid left-side donor hepatectomy: rationale for performing LADH.	World J Surg	38	1562-1563	2014
Tomimaru Y, Ito T, Kawamoto K, Hama N, Wada H, Kobayashi S, Eguchi H, Tanemura M, Mori M, Doki Y, Nagano H.	Clinical outcome of pancreas transplantation from marginal donors in Japan	Transplant Proc	46	954-957	2014
山下雅史、江口英利、和田浩志、富丸慶人、友國晃、濱直樹、川本弘一、丸橋繁、永野浩昭、土岐祐一郎、森正樹	Question72 C型肝炎ウイルスとスタチン・幹細胞癌との関連について	SURGERY FRONTEIR	21	319-321	2014
N.Marsuno, K.Uchida,H.Furukawa	Impact of Machine Perfusion Preservation of Liver Grafts From Donation After Cardiac Death.	TransplantationProceedings	46	1099-1103	2014
Furukori M, Imai K, Karasaki H, Watanabe K, Oikawa K, Miyokawa N, Taniguchi M, Furukawa H	Clinicopathological Features of Small Nonfunctioning Pancreatic Neuroendocrine Tumors.	Pancreatic neuroendocrine tumors	20 (47)	17949-17954	2014
Taniguchi M , Okizaki A ,Watanabe K ,Imai K ,Uchida K ,EinamaT , Shuke N ,	Hepatic clearance measured with technetium-99m-diethylenetriaminepenta-acetic	World Journal of Gastroenterology	20 (44)	16714-16720	2014

Miyokawa N , Furukawa H	acid-galactosyl human serum albumin single-photon emission computed tomography to estimate liver fibrosis.				
M.Taniguchi,H.Furukawa,T.Kawai,H.Morikawa,K.Morozumi,M.Goto,T.Kondo,A.Aikawa,T.Ito,A.Takahara,M.Nio,N.Kokubo,S.Uemoto,N.Fukushima,K.Yoshida,T.Kenmochi,H.Date,M.Ono,S.Eguchi,T.Shimamura,K.Mizuta,T.Yoshizumi,and T.Ueno	Establishmrny of Educational Program for Multiorgan Procurement From Deceased Donors.	Transplant Proceedings	46 (4)	1071-3	2014
川原敏靖, 古川博之	免疫抑制療法の進歩と展開	医学のあゆみ	252 (7)	820-821	2015
Yamasaki K, Tateyama M, Abiru S, Komori A, Nagaoka S, Saeki A, Hashimoto S, Sasaki R, Bekki S, Kugiyama Y, Miyazoe Y, Kuno A, Korenaga M, Togayachi A, Ocho M, Mizokami M, Narimatsu H, Yatsuhashi H.	Elevated serum levels of WFA+-M2BP predict the development of hepatocellular carcinoma in hepatitis C patients.	Hepatology	(5)	1563-70	2014
池田裕喜　奥瀬千晃 四柳宏	治癒が可能となったC型肝炎	HIV感染症とAIDSの治療	5巻2号	24－32	2014
四柳宏	C型肝炎ウイルスによる汚染事故への対処	化学療法の領域	30巻7号	1370－1372	2014

Ⅳ．研究成果の刊行物・別刷

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The Impact of Treated Bacterial Infections within One Month before Living Donor Liver Transplantation in Adults

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Background: The impact of treated preoperative bacterial infections on the outcome of living-donor liver transplantation (LDLT) is not well defined. The aim of this study was to determine the frequency of pre-transplant bacterial infections within one month before LDLT and their impact on the post-transplant morbidity and mortality.

Material/Methods: We retrospectively reviewed the records of 50 adult LDLT recipients between January 2009 and October 2011. Patients were divided into two groups based on whether they had episodes of bacterial infections within one month before LDLT.

Results: There were 20 patients who required antimicrobial therapy for pre-transplant infections. The pre-transplant infections comprised urinary tract infections (35%), cholangitis (10%), pneumonia (10%), bacteremia (5%), spontaneous bacterial peritonitis (5%), acute sinusitis (5%), subcutaneous abscess (5%), and empirical treatment (25%). Patients with pre-transplant infections had higher Child-Pugh scores [median, 11 *vs.* 9.5, $P<0.05$] and model for end-stage liver disease scores [median, 17.5 *vs.* 14, $P<0.05$] compared with the other patients. There were no correlations between the pathogens involved in the pre-transplant infections and those involved in post-transplant infections. The incidence of post-transplant infections was higher in the pre-transplant infection group within one week after LDLT, but was almost the same within one month after LDLT. The one-year survival rates were not significantly different between the groups.

Conclusions: Although pre-transplant infections are associated with a high risk of postoperative bacterial infection shortly after LDLT, they did not affect the short-term outcome when they had been appropriately treated before transplantation.

MeSH Keywords: Bacterial Infections • Liver Transplantation • Living Donors • Perioperative Care

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Background

Infection presents a higher risk when one considers the immunosuppression required by patients after transplantation. Therefore, patients with an active uncontrolled infection cannot undergo transplantation. Since deceased donor liver transplantation (DDLT) is usually performed as an emergent surgery, a preceding preoperative evaluation for occult infection cannot always be extensively performed. Despite this drawback of emergency surgery, some studies have revealed that histories of pre-transplant infections do not affect the outcomes of DDLT [1,2]. However, the outcomes of patients with pre-transplant infections have not been clarified in living donor liver transplantation (LDLT). Because of the shortage of deceased donors, LDLT has become an important therapeutic option for patients with end-stage liver disease. Since LDLT is generally performed as an elective surgery, it is possible to optimize the timing of transplantation depending on the recipient condition [3]. Patients and medical staff can make adequate preparations, including treatment for occult infections, before the operation. However, despite cautious preparation, patients may still develop pre-transplant infections, because patients with liver cirrhosis have increased susceptibility to bacterial infections and a risk of sepsis [1,4].

We usually perform LDLT as scheduled when the patients' pre-transplant infections have been cured with documentation of eradication before the operation. However, if pre-transplant infections affect the patient outcome in LDLT, it would be necessary to reconsider and postpone the operation. Since postponement of LDLT is often possible, clarifying the impact of pre-transplant infections on the post-LDLT outcomes is important.

The objectives of this study were to examine the details of the perioperative infections in LDLT recipients and to assess whether pre-transplant infections affect the early post-transplant outcome.

Material and Methods

We retrospectively analyzed 50 adult patients (27 males) who had undergone initial LDLT at Nagasaki University Hospital from January 2009 to September 2011. All transplantations were approved by the ethics committee of Nagasaki University Hospital.

Diagnosis of infections

Bacterial infections occurring within one month before LDLT were defined as pre-transplant infections in this study. Pre- and post-transplant infections were defined according to the criteria proposed by the Centers for Disease Control and Prevention [5].

Immunosuppression therapy

The standard immunosuppression regimen comprised tacrolimus and steroids. The trough level of tacrolimus was adjusted to 10–15 ng/ml until one month after surgery, and was tapered 10 ng/ml or less thereafter. Methyl prednisolone was administered at 1 g intravenously (i.v.) just before reperfusion during surgery. During the postoperative period, we administered methyl prednisolone at a dose of 0.5 mg/kg i.v. four times a day for the first three postoperative days, followed by 0.5 mg/kg twice a day for the next three days. Thereafter, the i.v. steroid was switched to oral prednisolone at 0.5 mg/kg once a day at seven days after transplantation, and the steroid was discontinued by three months after LDLT. Mycophenolate mofetil was added for ABO-incompatible LDLT cases and patients who were intentionally kept at lower trough levels of tacrolimus due to renal dysfunction.

Antimicrobial therapy

Antimicrobial prophylaxis comprised cefazolin (4 g/day) and ampicillin (4 g/day). These medications were started 30 minutes before laparotomy, and continued to be administered for 48 hours after the operation. The prophylaxis regimen was used for patients without pre-transplant infections and patients with pre-transplant infections who had completed treatment at the time of the operation.

Statistical analysis

The IBM SPSS Statistics 20 software program was used for the statistical analyses. The Mann-Whitney U test was used to analyze continuous data, and the chi-square test was used for categorical data. The overall survival was calculated with the Kaplan-Meier method, and data were compared with the log-rank test. A multivariate analysis using a Cox proportional hazards model was used to assess the factors predicting the survival rate one year after LDLT. We considered a value of $P<0.05$ to be statistically significant.

Results

The characteristics of patients

The indications for liver transplantation were liver cirrhosis due to hepatitis virus infection (n=34, 68%), primary biliary cirrhosis (n=4, 8%), primary sclerosing cholangitis (n=3, 6%), alcoholic liver cirrhosis (n=3, 6%), fulminant hepatic failure (n=2, 4%), and other diseases (n=4, 8%). Twenty patients (40%) had pre-transplant infections. Patients with pre-transplant infections had higher model for end-stage liver disease (MELD) scores (median=17.5 *vs.* 14, P<0.05) and Child-Pugh

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Table 1. Characteristics of patients.

	Pretransplant infections				*P* Value
	(+) n=20		(–) n=30		
Age	55	(30–72)	55	(27–72)	0.789
Gender, male	7	(35%)	20	(66%)	0.028
MELD score	17.5	(9–43)	14	(7–27)	0.028
Child-Pugh score	11	(6–15)	9.5	(5–13)	0.018
Hepatitis virus infection	8	(40%)	26	(87%)	<0.01
Cholestatic liver disease	6	(30%)	1	(3.3%)	0.012
HCC	6	(30%)	21	(70%)	<0.01
Operaion time (min)	802.5	(598–1159)	802	(654–1129)	0.961
Blood loss (ml)	5700	(1120–17600)	4150	(520–18400)	0.075
Pretransplant dialysis	4	(20%)	1	(3%)	0.076
Pretransplant ICU stay	3	(15%)	1	(3.3%)	0.170
Left lobe graft	17	(85%)	20	(66%)	0.131
Hepaticojejunostomy	4	(20%)	1	(3.3%)	0.076
Incompatible ABO blood type	2	(10%)	4	(13.3%)	0.544
Post LDLT ICU stay (days)	5	(1–36)	7	(2–20)	0.259
Post LDLT hospital stay (days)	47.5	(16–195)	47.5	(17–140)	0.513

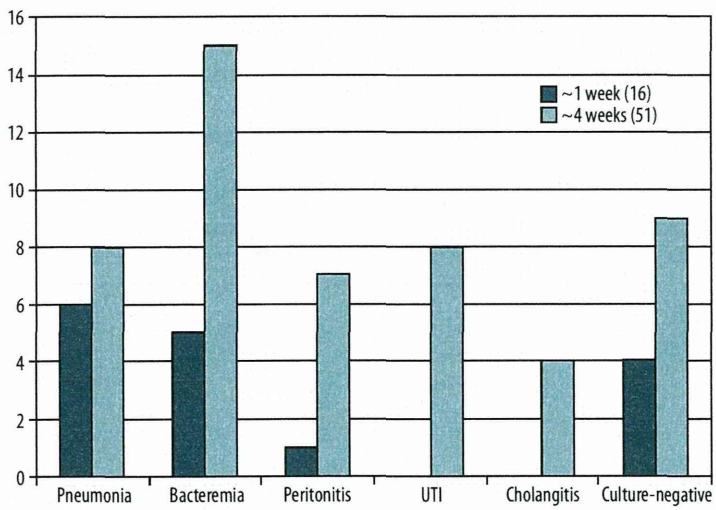

Figure 1. A comparison of the types of infections after LDLT. Pneumonia was the most common infection that occurred within one week after LDLT. UTI and cholangitis were not detected during this period. On the other hand, bacteremia was the most common infection one month after LDLT.

scores (median=11 *vs.* 9.5, P<0.05) than patients without infections. The rates of hepatitis virus infections (40% *vs.* 87%, P<0.01) and hepatocellular carcinoma (30% *vs.* 70%, P<0.01) were lower in the pre-transplant infection group. These patients also had more cholestatic liver diseases, which included primary biliary cirrhosis and primary sclerosing cholangitis (30% *vs.* 3.3%, P=0.01). There were no significant differences in other indications (Table 1).

Pre-transplant infections

The pre-transplant infections comprised urinary tract infections (UTI) (n=7, 35%), cholangitis (n=2, 10%), pneumonia (n=2, 10%), bacteremia (n=1, 5%), spontaneous bacterial peritonitis (SBP) (n=1, 5%), acute sinusitis (n=1, 5%), and subcutaneous abscess (n=1, 5%). The other five patients (25%) did not completely match the criteria proposed by the Centers for

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Table 2. The details of post-transplant infections.

Infection/Pathogens	0–1 week	–1 month	N
Bacteremia	**5**	**10**	**15**
Pseudomonas aeruginosa	2	4	6
Enterococcus faecium	1	1	2
Acinetobacter baumannii		1	1
Bacteroides fragilis	1		1
Enterobacter cloacae		1	1
Escherichia coli		1	1
Klebsiella pneumoniae		1	1
MRCNS	1		1
Staphylococcus epidermidis		1	1
Pneumonia	**6**	**2**	**8**
Staphylococcus epidermidis	2		2
Enterobacter cloacae	1		1
Klebsiella pneumoniae	1		1
MRSA	1	1	2
Pseudomonas aeruginosa	1	1	2
UTI	**0**	**8**	**8**
Enterococcus faecium		3	3
Klebsiella pneumoniae		2	2
Citrobacter freundii		1	1
MRCNS		1	1
Staphylococcus epidermidis		1	1
Peritonitis	**1**	**6**	**7**
Enterococcus faecium	1		1
Enterococcus faecalis		2	2
Pseudomonas aeruginosa		2	2
Enterococcus raffinosus		1	1
Staphylococcus epidermidis		1	1
Cholangitis	**0**	**4**	**4**
Enterococcus faecium		4	4
Culture-negative	**4**	**5**	**9**

MRCNS – methicillin-resistant coagulase negative staphylococci; UTI – urinary tract infection.

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Table 3. Incidence of post-transplant infections.

	Pre-transplant infections				*P* Value
	(+) N=20		(–) N=30		
Within 1 week after LDLT	10	(50%)	6	(20%)	0.028
Within 2 weeks after LDLT	15	(75%)	16	(53%)	0.105
Within 1 month after LDLT	17	(85%)	19	(63%)	0.087

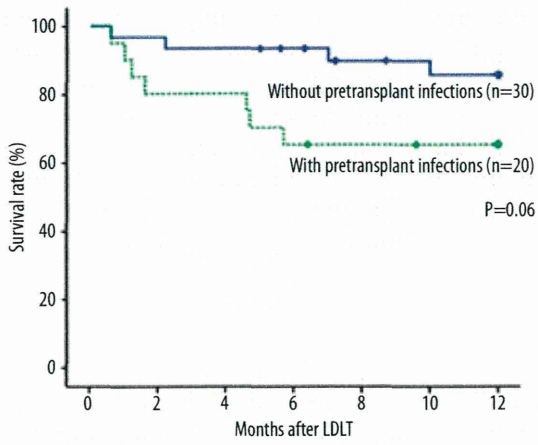

Figure 2. The survival rates of patients with and without pre-transplant infections. The one-year survival rate was lower in the pre-transplant infection group, but the difference was not significant (86% *vs.* 65%, P=0.06).

Disease Control and Prevention [5]. However, all five patients were diagnosed to have bacterial infections based on their clinical status (fever, chills and elevated levels of inflammatory parameters), and thus were treated empirically. The clinical conditions of all patients improved rapidly after the administration of antimicrobial therapy. No patients had combined episodes of infection. Pathogens were detected in 11 of 20 patients (12 pathogens). *Escherichia coli* was the most common pathogen in the pre-transplant period (n=6), followed by *Enterococcus faecium* (n=2), *Enterococcus avium* (n=1), *Proteus mirabilis* (n=1), *Streptococcus epidermidis* (n=1), and Methicillin-resistant *Staphylococcus aureus* (n=1).

Post-transplant infections

Of the 50 patients, 16 patients (16 episodes) developed post-transplant infections within one week after LDLT. Pneumonia was the most common infection during this period. On the other hand, 36 of the 50 patients (51 episodes) had post-transplant infections within one month after LDLT. Bacteremia was the most common infection during this period (Figure 1). The details of the causative bacterial pathogens after LDLT are shown in Table 2. Among the patients with pre-transplant infections, the previous pathogens were not found after LDLT in any of the patients. The post-transplant infection rate was significantly higher in the pre-transplant infection group during the first week after LDLT (50% *vs.* 20%, P<0.05), but was not significantly different within one month after LDLT (85% *vs.* 63%) (Table 3).

Patient outcomes

The one-year survival rate tended to be lower in the pre-transplant infection group (65% *vs.* 86%, P=0.06; Figure 2). A multivariate analysis showed that a higher MELD score (P<0.05) was a significant risk factor for a decreased one-year survival after LDLT (Table 4). A pre-transplant infection did not significantly adversely affect the one-year survival after adjusting for other factors.

Table 4. Multivariate analysis for 1 year survival.

Variable	HR (95% confidence interval)		*P* Value
Age (>60)	3.77	(0.34–41.67)	0.279
MELD (>20)	28.38	(1.40–576.45)	0.029
Child-Pugh (>9)	1.81	(0.21–15.57)	0.587
Hepatitis virus infection	1.62	(0.23–11.61)	0.633
HCC	6.91	(0.64–74.90)	0.112
Incompatible ABO blood type	0.17	(0.010–2.77)	0.210
Pretransplant infections	2.77	(0.43–18.02)	0.286

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Discussion

In the study, we found that the presence of bacterial infections prior to LDLT was not a risk factor for bacterial infections developing during the first month after LDLT. The one-year survival rate was lower in the pre-transplant infection group, but the rates were not significantly different. We thought that the tendency might have been based on the differences in the background of the patients, because those with pre-transplant infections had higher Child-Pugh scores and MELD scores. In fact, the MELD score was the only significant risk factor for the one-year survival in this study.

Surgical outcomes are largely influenced by the pre-surgical conditions [6], and the MELD score has a crucial role in predicting early postoperative mortality after DDLT [3,7]. The same result was also reported in LDLT [8,9]. However, other studies have concluded that the MELD score had no correlation with graft or patient survival [10–12]. We found that a MELD score >20 was associated with a lower one-year survival rate.

The studies concerning the effects of pre-transplant bacterial infections have been limited. One study showed that patients with an episode of pre-transplant SBP had a higher incidence of post-transplant complications, infections, and early transplant mortality [13]. On the other hand, three studies concluded that a pre-transplant SBP history did not affect the post-transplant outcome [2,14,15]. Sun et al. divided their 100 DDLT cases into two groups; a pre-transplant infection group (32/100) and a non-infection group (68/100). They concluded that pre-transplant infections were not a significant risk factor for poor outcomes if the post-transplant infections were adequately treated [1]. Our study evaluated the influence of preoperative infections in LDLT cases for the first time. Despite the difference in their backgrounds, our results were almost the same as the previous reports which examined DDLT patients. Interestingly, patients with pre-transplant infections had more infectious episodes within one week after LDLT. We could not determine the reason for this phenomenon, but it might reflect the poorer general condition of the patients at the time of transplantation. On the other hand, since no patient exhibited a recurrent infection with the pre-transplant pathogens in the early post-operative period, we considered that the pre-transplant infections were successfully treated and the post-transplant infections were all new. This result suggested that the treatment of pre-transplant pathogens did not need to be continued in the post-transplant period. To improve the rate of early detection of post-transplant infections, patients should be recognized as a group at high risk of bacterial infections. The duration of antimicrobial prophylaxis, timing of immunosuppressant therapy, and the loading doses should be intensively discussed considering the patient's condition.

Conclusions

Pre-transplant infections did not affect the incidence of post-transplant infections within one month after LDLT, and did not affect the one-year survival rate. However, pre-transplant infections were associated with a high risk of post-transplant infection within the first week after LDLT.

Statement

The authors declare no conflict of interest. This work was not funded by any educational or commercial organization.

References:

1. Sun HY, Cacciarelli TV, Singh N: Impact of pretransplant infections on clinical outcomes of liver transplant recipients. Liver Transpl, 2010; 16: 222–28
2. Mouzer R, Malik SM, Nasr J et al: Spontaneous bacterial peritonitis before liver transplantation does not affect patient survival. Clin Gastroenterol Hepatol, 2010; 8: 623–28
3. Saab S, Wang V, Ibrahim AB et al: MELD score predicts 1-year patient survival post-orthotopic liver transplantation. Liver Transpl, 2003; 9: 473–76
4. Foreman MG, Mannino DM, Moss M: Cirrhosis as a risk factor for sepsis and death: analysis of the National Hospital Discharge Survey. Chest, 2003; 124: 1016–20
5. Garner JS, Jarvis WR, Emori TG et al: CDC definitions for nosocomial infections, 1988. Am J Infect Control, 1988; 16: 128–40
6. Clavien PA, Barkun J, de Oliveira ML et al: The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg, 2009; 250: 187–96
7. Habib S, Berk B, Chang CC et al: MELD and prediction of post-liver transplantation survival. Liver Transpl, 2006; 12: 440–47
8. Marubashi S, Dono K, Asaoka T et al: Risk factors for graft dysfunction after adult-to-adult living donor liver transplantation. Transplant Proc, 2006; 38: 1407–10
9. Kaido T, Egawa H, Tsuji H et al: In-hospital mortality in adult recipients of living donor liver transplantation: experience of 576 consecutive cases at a single center. Liver Transpl, 2009; 15: 1420–25
10. Hayashi PH, Forman L, Steinberg T et al: Model for End-Stage Liver Disease score does not predict patient or graft survival in living donor liver transplant recipients. Liver Transpl, 2003; 9: 737–40
11. Yi NJ, Suh KS, Lee HW et al. Improved outcome of adult recipients with a high model for end-stage liver disease score and a small-for-size graft. Liver Transpl, 2009; 15: 496–503
12. Wai CT, Woon WA, Tan YM et al: Pretransplant Model for End-stage Liver Disease score has no impact on posttransplant survival in living donor liver transplantation. Transplant Proc, 2012; 44: 396–98
13. Ukah FO, Merhav H, Kramer D et al: Early outcome of liver transplantation in patients with a history of spontaneous bacterial peritonitis. Transplant Proc, 1993; 25: 1113–15
14. Altman C, Grangé JD, Amiot X et al: Survival after a first episode of spontaneous bacterial peritonitis. Prognosis of potential candidates for orthotopic liver transplantation. J Gastroenterol Hepatol, 1995; 10: 47–50
15. Van Thiel DH, Hassanein T, Gurakar A et al: Liver transplantation after an acute episode of spontaneous bacterial peritonitis. Hepatogastroenterology, 1996; 43: 1584–88

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LIVER TRANSPLANTATION 21:266–268, 2015

LETTER FROM THE FRONTLINE

Preoperative Simulation With a 3-Dimensional Printed Solid Model for One-Step Reconstruction of Multiple Hepatic Veins During Living Donor Liver Transplantation

Received July 7, 2014; accepted October 6, 2014.

TO THE EDITORS:

A 53-year-old male patient underwent living donor liver transplantation (LDLT) for hepatitis C virus–infected liver cirrhosis complicated with hepatocellular carcinoma. Preoperative 3-dimensional (3D) images were obtained with a 3D image analysis system (Synapse Vincent; Fujifilm Medical, Tokyo, Japan) so that we could evaluate the graft volume and possible congested volume after implantation in LDLT. This revealed that a large middle hepatic vein (MHV) drained a vast area in the right lobe (Fig. 1A,B). The estimated volume of the donor's whole liver was 1048 mL. The extended left graft was considered to be small for the size of the recipient and corresponded to 30% of the recipient's standard liver volume; also, it had an estimated congested area of 407 mL, which was equivalent to 39% of the donor's liver volume in the remnant right lobe (Fig. 1C). As a result, if a left lobe graft could be procured, the functional remnant liver volume was estimated to become 20% of the donor's liver volume. Hence, the left lobe was considered inappropriate not only because of the small-for-size graft for the recipient but also because of safety concerns for the donor.

After ensuring sufficient drainage of the left lobe by medial segmental vein (V4) and the left hepatic vein, we decided to use a right lobe graft with the MHV because the volume was considered sufficient and was equivalent to 47.5% of the standard liver volume of the recipient. A preoperative contrast-enhanced computed tomography scan revealed a distance of 2 cm between the donor's right hepatic vein (RHV) and MHV at the estimated Cantlie line. Because of the location and alignment, we planned to use an autologous portal vein (PV) Y-graft interposition for the hepatic vein anastomosis. The image of the Y-graft from the recipient's PV was also made with the Synapse Vincent program (Fig. 2).

An extended right lobe graft was transplanted from the patient's wife, and the actual graft weight was 493 g, which corresponded to 42.3% of the recipient's standard liver volume. A hilar PV was harvested from the recipient, and ex vivo hepatic vein reconstruction was performed through the connection of a right portal branch to the MHV and a left portal branch to the RHV with continuous 5-0 polypropylene monofilament sutures. An end-to-end anastomosis was performed between the explanted main PV graft and the inferior vena cava with continuous 5-0 polypropylene monofilament sutures. In addition, the right inferior hepatic vein (RIHV) was directly anastomosed to the inferior vena cava. After reperfusion, intraoperative Doppler ultrasound showed a stable and sufficient hepatic inflow and outflow from the 3 anastomosed hepatic veins. The length of the recipient operation was 13 hours 15 minutes, and the blood loss was 11,700 g. At the time of this writing, 8 months after LDLT, the patient was doing well with good liver function. The fact that both the MHV and the RHV were patent in the early postoperative period is considered to have contributed to the patient's recovery. The donor favorably recovered without any complications. The study protocol received a priori approval by the appropriate institutional review board committee.

DISCUSSION

An extended right lobe graft is uncommon in Japan because of concerns about donor safety. On the other hand, approximately 58% of individuals have an MHV that is larger than or the same size as the RHV, and in 13% of right liver lobes, the MHV partially or totally drains a vast area, including segment 6,[1] as with our patient. A preoperative 3D image simulation depicting

Potential conflict of interest: Nothing to report.

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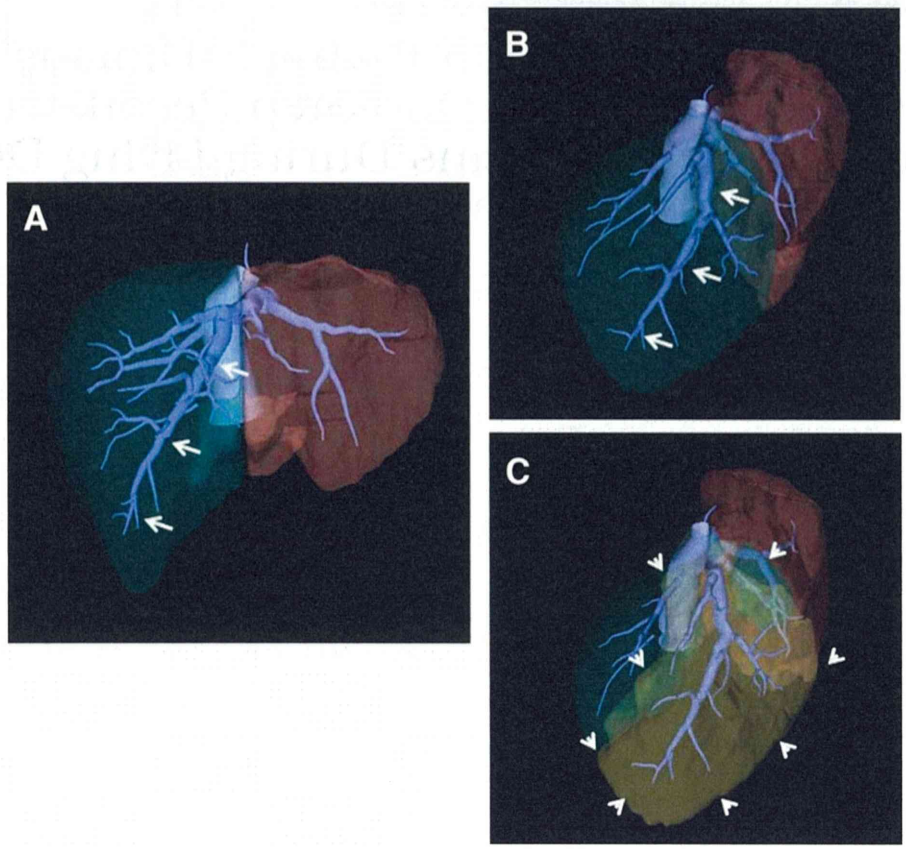

Figure. 1. (A,B) A preoperative 3D image evaluation of the donor's graft revealed that the large MHV drained a vast area in the right lobe (arrows). (C) The estimated volume of the congested area (the yellow area with arrowheads) was 407 mL, which was equivalent to 39% of the donor's liver volume in the remnant right lobe.

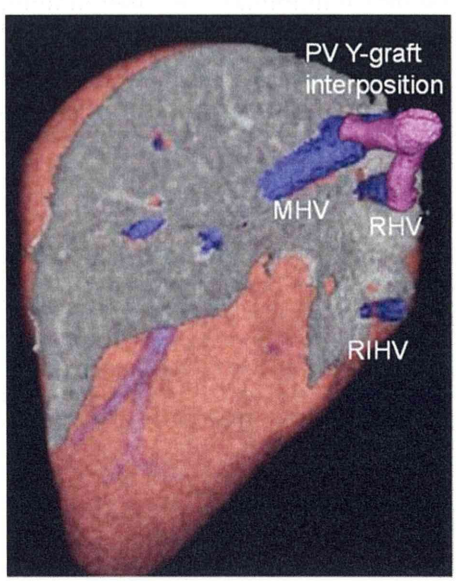

Figure. 2. A preoperative 3D simulation of the autologous PV Y-graft interposition for the hepatic vein anastomosis connecting a right portal branch to the MHV and a left portal branch to the RHV was performed with the Synapse Vincent program.

the anatomy in detail and providing an accurate estimate of the possible congested volume prompted us to make the decision to use an extended right lobe graft in this case.

The usefulness of explanted autologous PV grafts for hepatic vein tributaries in LDLT has recently been reported.[1,2] Although previous reports have described the use of a PV graft for MHV tributaries, including segment 5 and 8 veins, in our case, both main drainage veins, including the MHV and the RHV, were reconstructed with an interposition Y-shaped PV graft. Subsequently, the main outflow of the liver graft depended on this reconstruction. The reconstruction of the main drainage veins of the right liver graft with an explanted hilar PV graft is considered to be an effective management strategy for cases with a large distance between the hepatic veins in LDLT.

The useful application of a 3D volume analyzer in the field of liver surgery has recently been reported.[3,4] Meticulous preoperative volumetry of the partial liver graft is essential in terms of both postoperative graft function and donor safety. One of the strongest merits of using a 3D volume analyzer is that it is possible to