Annual Review

消化器

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1. 肝炎・肝癌の疫学

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key words　liver cancer, HBV carrier, HCV carrier, hepatitis virus screening test

動　向

平成23年時点のわが国における「肝」（肝および肝内胆管）の悪性新生物による死亡は31,875人と，前年に比べ約900人減少したが，依然として部位別にみた悪性新生物による死亡数の上位から4番目に位置している．男性の肝癌死亡は女性の約2倍高値であり，2002年以後に若干の減少傾向が認められるが，女性は微減している．

わが国の肝細胞癌死亡の約8～9割は，B型肝炎ウイルス（HBV）あるいはC型肝炎ウイルス（HCV）の持続感染に起因し，肝細胞癌死亡全体の約7割はHCVの持続感染に起因する．一方，2000年以後，非B非C型に由来する肝癌の割合が全体の10～15%を占め徐々に増加傾向にあり，その原因や動向についてNASH（non-alcoholic steatohepatitis）との関連性が示唆されている．

A. 肝癌発生数と肝癌のetiology

わが国の死因の上位を占める疾病は昭和56年以降ほぼ30年にわたり悪性新生物が死因第1位を占めているが，最新の平成23年人口動態統計資料[1]によると，1位悪性新生物，2位心疾患，3位肺炎，4位脳血管疾患となり，脳血管疾患が肺炎とわずかの差で順位が入れ替わった．総死亡数1,253,066人のうち，悪性新生物357,305人（28.5%），心疾患194,926人（15.6%），肺炎124,749人（10.0%），脳血管疾患123,867人（9.9%）であり，四大死因により全死亡数の65%を占めている．

悪性新生物による死亡は，高齢化の影響を受けているため，粗死亡率では男女とも一貫して増加傾向にあるが，昭和60年人口を標準集団とした年齢調整死亡率では，男女とも，部位による相異はあるが減少傾向が認められている．医学・医療技術の進歩や種々の予防政策による発癌ハイリスク集団の減少などが考えられる．

部位別にみた悪性新生物による死亡の順位をみると，男性では肺，胃，大腸（結腸と直腸S状結腸移行部および直腸），肝，膵の順であり，女性では大腸，肺，胃，膵，乳房，肝である．悪性新生物による死亡総数約35.7万人のうち，肺7.0万人，胃5.0万人，大腸4.5万人，肝3.2万人（男性20,972人，女性10,903人）である．

図1に，毎年集計報告されている人口動態統計[2]を基にした肝癌による死亡の推移を示す．

日本における肝癌死亡は1950年代はじめから1970年代半ばまでは人口10万人あたり10人前後（死亡実数は1万人以下）であったが，その後

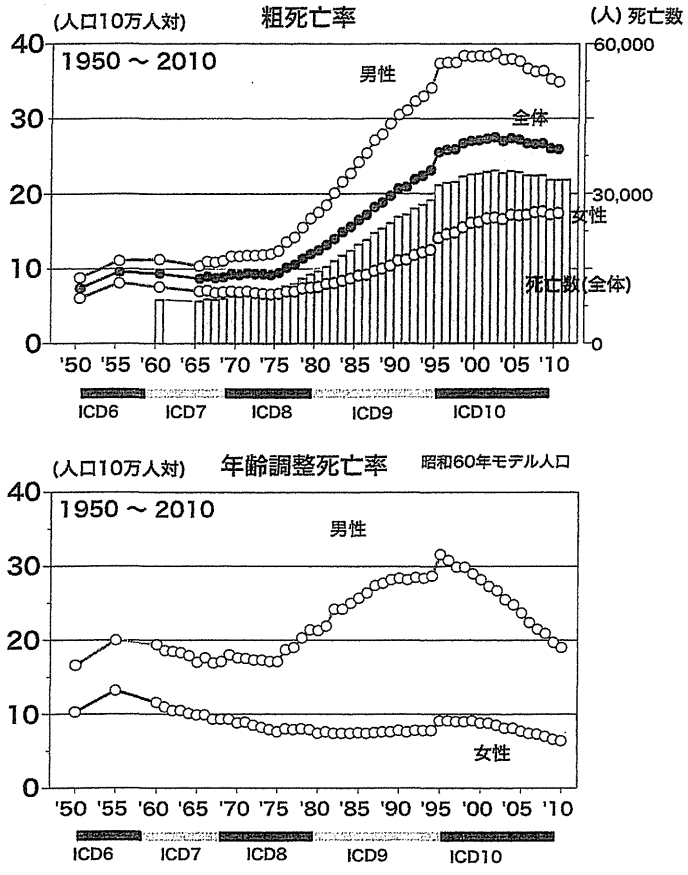

図1　わが国における肝癌による死亡の推移
(昭和50年～平成21年人口動態統計[2])

増加し，2002年に人口10万対27.5のピークを示した後，若干の減少あるいは横ばい状態を保っている．男女別にみると，男性の肝癌死亡は女性の約2倍の高値を示してきたが，2002年より減少傾向が認められている．また，女性は微減している[3]．

肝癌の成因については，日本肝癌研究会調査成績[4] と人口動態統計資料の肝癌死亡数とを用いた田中ら[3] による病因別にみた肝癌死亡の推移を示す（図2）．HBVの持続感染に起因する肝癌の死亡割合は1980年代から現在にいたるまで10万人対3～4人と増減なくほぼ一定の値を示している．これまでのHBV感染の主な感染経路は母子感染の比重が大きかったことから，HBV母子感染防止事業（1986年以後出生のすべての児を対象とした公費負担によるHBV母子感染防止事業）の効果により該当世代のHBs抗原陽性率が低下したことを考えると，図2に示したHBVの持続感染に起因する肝癌死亡10万人対3～4人は，当該防止事業開始以後に出生した世代が肝発癌年齢を迎える今から10～20年後から徐々に減少すると推察できる．

一方，1970年代から2000年代にかけて肝細胞癌による死亡が増加した原因は非A非B型によるものであるが，HCV感染の診断が可能となった1992年以降の状況から，そのほとんどがHCVの持続感染によるものであることが明らかとなった．なお，2000年以降，非B非C型に由来する

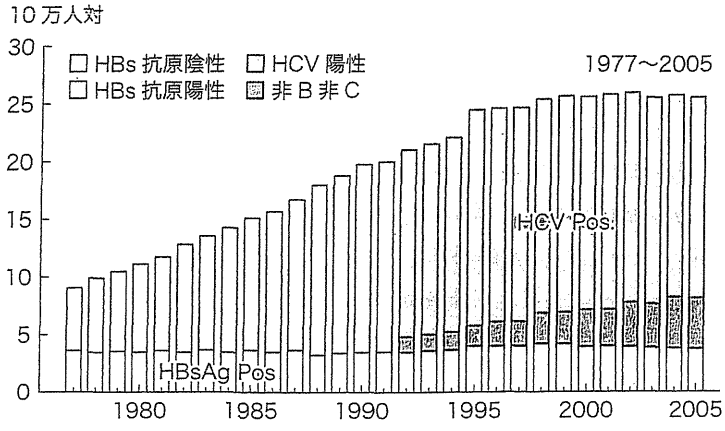

図2　肝癌による死亡数の経年的推移
（厚労省 肝炎等克服緊急対策研究事業「肝炎ウイルス感染状況・長期経過と予後調査及び治療導入対策に関する研究」班より，試算：May, 2011 J.Tanaka）

肝癌による死亡の割合が徐々に増加の傾向にあり，非アルコール性脂肪性肝疾患（NASLD）など非感染性肝疾患との関連が示唆されている[5-7]．Tokushigeら[8]の調査による14,530例の肝細胞癌（hepatocellular carcinoma: HCC）の内訳は，HBV14.1%，HCV66.3%，HBVとHCVの重複感染は3.7%，アルコール性7.2%，NAFLD2.0%と報告されている．

このように近年日本においてもNASHに関連した肝硬変や肝癌が増加しているものの，依然として肝癌死亡の14%がHBVの，約70%がHCVの持続感染に起因すると考えられることから，肝癌対策を構築する上でも，肝炎ウイルス持続感染者（肝炎ウイルスキャリア）の規模の把握や治療を含む対策および感染予防対策が効果的であると考えられる．

世界における肝癌の罹患状況をみると，El-Serag[9]は，悪性新生物に罹患した患者のうち，肝癌は男性では5位52万3千人（7.9%），女性では7位22万6千人（6.5%）と推計している(2008)[9,10]．一方，国立がん研究センターの資料[11]（2005年）によると日本の肝癌罹患者数は，癌罹患症例のうち男性では28,729人（7.4%），女性では，13,465人（5.5%）であり，男性は女性の2倍の肝癌罹患（発生）が認められている．

肝癌の生存率を高く維持するためには多岐にわたる診療科を含めた高度な医療技術と共に充実した保険医療制度などが必要となるため，一部の先進国を除くと，世界の地域別にみた肝癌死亡率はその地域の肝癌の罹患率（発生率）と類似した値を示している．また，肝癌の発生リスクは，食物やアルコールのリスクと比べて，肝炎ウイルスの持続感染によるリスクが大きく占めるので，地域別にみた肝癌罹患状況は肝炎ウイルス感染率（罹患率および有病率）にも関連しているといえる．肝癌は世界的にみると85%が発展途上国に集積し，特に，サハラ砂漠以南のアフリカと東アジアで多く認められている[10]．年齢調整した肝癌罹患率は，東アジアでは10万人年対30以上，南ヨーロッパでは10万人年対10～20と推定されているが，北アメリカ，南アメリカ，北ヨーロッパおよびオセアニアでは10万人年対5以下の低い値となっている（2008年）[9,12]．また，肝癌罹患率にはいずれも地域も男女差が認められるが，特に

高度侵淫地区において著しいとの指摘もある.

肝癌の成因については，肝癌症例に占めるHBs抗原陽性率（HBVキャリア率）を比較した報告[9]があり，スウェーデンでは3%，アメリカでは10%，日本では10～15%，ギリシアでは55%，韓国では70%と推計されている．また，これまで肝癌罹患率が低いとされていた地域でも近年，肝癌の罹患率が増加しているという報告がある（アメリカ[13]，カナダ[14]，ヨーロッパ[15]）．なお，肝癌と診断される年齢は，中国では平均して55～59歳に，欧米では63～65歳との報告があるが，これは病因ウイルスの相異（HBV, HCV）やgenotypeの相異と共に他のリスクファクターの存在も関与していると考えられる.

B. 肝炎ウイルスキャリア数

わが国では，肝炎ウイルスの持続感染に起因する肝癌死亡が8割を占めることから，肝炎ウイルス持続感染者数（肝炎ウイルスキャリア数）を把握し社会に及ぼす規模を測ることが肝癌対策の根幹となる.

肝炎ウイルスキャリア数の把握は，2000年以後に得られた2つの大規模集団の特性を考慮した上で算出したHBs抗原陽性率およびHCVキャリア率を用いてTanakaら[16]がHBVキャリア数およびHCVキャリア数を推計している．二つの大規模集団とは，日本赤十字血液センターにおける初回供血者3,748,422人，および肝炎ウイルス検診の節目検診受診者；HBV検診6,280,111人，HCV検診：6,304,276人である.

その結果をみると，HBVキャリア数は903,145人（95%CI: 83.7～97.0万人），HCVキャリア数は807,903人（95%CI: 68.0～97.4万人）と推計されている．これらの値は，初回供血者集団および肝炎ウイルス検診受診者集団におけるキャリア率からの推計値であることから，自身が感染を知らないまま潜在しているキャリアの推計数に相当している.

社会に存在する肝炎ウイルスキャリア数の把握には，「患者としてすでに通院・入院しているキャリア」数と，「感染を知ったが受診しないでいる，あるいは継続受診に至っていないキャリア」数の算出が残されている．厚労省疫学研究班でも，患者調査および他の調査を併せ用いた推定研究を行っているところであるが，前者は50～100万人と中間報告[17]がある.

一方，国外における肝炎ウイルスキャリア数，キャリア率についてみると，近年，HCV感染に起因した肝癌が増加傾向[18,19]にあるとの報告が多いアメリカでは，1945～1965年出生コホート集団のHCV抗体陽性率が3.25%（95% CI: 2.80–3.76）と高値であり，この集団が肝発癌年齢にさしかかっていることが報告されている[20].

また，アメリカでは全人口の1～2%に相当する肝炎ウイルスキャリアが存在し，80万人から140万人がHBVキャリアであること，270万人から390万人がHCVキャリアであると見積もられ[21]ているが，多くは自身の感染を知らずに社会に潜在している[22]．Spradlingは，The National Health and Nutrition Examination Survey（NHANES）の結果と125万人の検診受診者のデータを比較し，半数のHCVキャリア，20%のHBVキャリアが未だ感染を知らずに社会に潜在している状態であると推定[23]した．アメリカではCenters for Disease Control（CDC, Atlanta）が中心となって肝癌のリスク集団の拾い上げの方策[24]として1945～1965年出生の年齢層（baby-boomer generation）を対象として2012年5月から肝炎ウイルス検査を開始している．これは，世界に先駆けて2002年から住民を対象に実施された節目・節目外肝炎ウイルス検診の目的と一致している.

WHOの推計[25]によると，毎年300～400万

人が新たにHCVに感染し，地域によって感染率は異なるものの，全体では2%程度，約1億5千万人がHCVの持続感染状態であると見積もられている．一方，HBVの感染者は20億人にのぼり，HBV持続感染者は3.5億人，世界人口の4分の3は高度感染地に居住している．毎年，35万人以上の人々がHCV関連肝疾患により，約60～100万人以上の人々がHBV関連肝疾患により死亡していると推定されている．

C. 肝炎・肝癌対策

わが国の社会生活全般における肝炎ウイルス感染の発生要因が徐々に減少し，若い世代におけるHBVキャリア率やHCVキャリア率は低い値を示すに至っている．「肝炎対策基本法」（2009年12月）を基盤として，すでに感染しているキャリアへの対策，具体的には，肝炎ウイルス検査の推進，肝疾患診療ネットワークの構築，新規治療法の開発に加え，肝炎患者の経済的負担の軽減や抗ウイルス療法の受療推進のための医療費助成制度等の事業等が積極的に進められている．このように日本では，世界に先駆けて肝炎ウイルス持続感染者の規模の把握や治療を含めた肝炎ウイルスキャリア対策が実施されてきているといえる．

エジプトは15歳から59歳の年齢層でのHCVキャリア率が10%を超え世界中で最も高いことが知られている．一般集団でのHCV新規感染率は1000人年あたり2.4人，年間165,000人のHCVキャリアが新たに発生している状況の中で，透析患者でのHCV新規感染率を現状28%から6%にまで減らすこと，2012年6月までにはHCVキャリアに対して肝炎治療を行うことができる約19万人規模の医療施設を整備すること等，2008年より国を挙げた対策が進められている[26-30]．

肝炎・肝癌対策をその病因論的また疫学的視点から捉えた場合，その地域のprevalence, incidenceの状況や診療ネットワーク・医療環境を把握した上で，適切な対策が求められる．

わが国がこれまで行ってきた肝炎ウイルス感染の動向調査・感染防止対策を継続しつつ，社会における肝炎ウイルスキャリアの存在状態別にそれぞれの課題を掲げて具体的な対策を推進することが肝癌対策にとっても重要であるといえる．

肝炎対策の先進国であるわが国は，肝癌対策の新たな局面を迎えていると考えられる．

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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Prognostic Significance of Antithrombin III Levels for Outcomes in Patients with Hepatocellular Carcinoma After Curative Hepatectomy

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ABSTRACT

Background. Although several studies have shown that serum antithrombin III (ATIII) has anti-inflammatory effects, the prognostic value of ATIII in HCC is unknown. We investigated the influence of preoperative ATIII levels on the outcome of patients who underwent hepatectomy for hepatocellular carcinoma (HCC).

Methods. Data from 440 patients (314 patients with ATIII $\geq$70 % and 126 patients with ATIII <70 %) who underwent curative hepatectomy for HCC were retrospectively collected and analyzed. To overcome bias due to the different distribution of covariates for the 2 groups, propensity score matching was performed on the patients, and outcomes were compared.

Results. The propensity score analysis revealed that 65 patients with ATIII of $\geq$70 % (group 1) and 65 patients with ATIII of <70 % (group 2) had the same preoperative and operative characteristics (excluding the ATIII level). The overall survival rate and the disease-free survival rate was significantly higher in group 1 than in group 2 ($P = 0.005$ and 0.011, respectively). Multivariate analysis showed that ATIII was a significant favorable factor for overall survival and disease-free survival of patients with HCC after curative hepatectomy.

Conclusions. The prognosis of patients with HCC was found to be associated with preoperative antithrombin III levels. ATIII may be useful for predicting outcomes of patients with HCC after curative hepatectomy.

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Hepatic resection is a well-accepted therapy for hepatocellular carcinoma (HCC), but many patients develop cancer recurrence, with the cumulative 5-year HCC recurrence rate being over 60 %.[1,2] A high incidence of tumor recurrence after hepatic resection remains a major drawback. The risk factors for prognosis after resection of HCC have been extensively studied.

Antithrombin III (ATIII) is a heparin-binding protein and a major inhibitor of coagulation proteases, primarily thrombin and factor Xa.[3] ATIII has been reported to efficiently inhibit tumor angiogenesis in a mouse model.[4,5] In clinical settings, decreased plasma ATIII levels have been described in a variety of different cancers, including lung, colon, ovary, and prostate cancers.[6–8] However, few data are available on the impact of ATIII on outcomes of patients with HCC who underwent hepatectomy.

In this study, we aimed to investigate the effect of ATIII on survival and HCC recurrence in patients who underwent curative hepatic resection by both methods of one-to-one match study using propensity score and multivariate analysis.

METHODS

Between the years 2000 and 2008, a total of 440 patients with HCC underwent curative hepatectomy as an initial treatment at the Department of Gastroenterological Surgery, Hiroshima University Hospital, Hiroshima, Japan. The study was approved by the concerned institutional

review boards. Written informed consent was obtained from all patients. The patients were categorized into 2 groups on the basis of their preoperative ATIII level: ≥70 % (group 1, $n = 314$), and <70 % (group 2, $n = 126$).

The type of hepatectomy selected was based on liver function and tumor extent.[9,10] Liver function was assessed by the Child-Pugh classification and the indocyanine green retention rate at 15 minutes (ICG-R15).[11] If the liver function was sufficient, anatomic resection (segmentectomy, sectionectomy, or hemihepatectomy) was performed.[12,13] In patients with insufficient hepatic reserve, limited resection was performed. For example, right hemihepatectomy could be tolerated if the ICG-R15 was in the normal range. One-third of the liver parenchyma could be resected for patients with ICG-R15 of 10–19 %, segmentectomy was possible for patients with ICG-R15 of 20–29 %, and limited resection was possible for patients with ICG-R15 of ≥30 %.[10] Hepatectomy was performed using procedures described by Itamoto et al.[9] Postoperative follow-up included liver function tests, serum alfa-fetoprotein (AFP), hepatic ultrasonography on a 3-month basis, and computed tomographic scans every 6 months. Follow-ups were performed in outpatient clinics or by the patients' general practitioner. Patients with intrahepatic recurrence were managed with ablative therapies such as radiofrequency ablation and percutaneous ethanol injection therapy, transarterial chemoembolization (TACE), or surgery, including living donor liver transplantation. Data were updated until June 2011 and survival was computed from the date of the initial surgery.

Definitions

Normal ATIII is defined as a level of ≥70 % in this study, because it has been shown that anti-thrombin activity of heparin was significantly decreased in the serum ATIII level-dependent manner when plasma ATIII levels were <70 %.[14,15] Major hepatectomy was defined as the resection of 3 or more Couinaud segments. Curative hepatectomy was defined as the removal of all recognizable tumors. All postoperative complications were reviewed for at least 30 days after surgery. The complications were graded according to the method described by Clavien et al.[16] Complications were considered morbid if they were of grade IIIA or greater. Postoperative mortality was defined as any death that occurred within 30 days of surgery.

Receiver-Operating Characteristic (ROC) Analysis

ROC curve analysis was performed to determine the optimal cutoff values for subsequent analyses. Each cutoff value was determined by seeking the most optimal combination of high sensitivity and specificity values, while maintaining the lowest likelihood ratio of a negative test and the highest likelihood ratio of a positive test.

Statistical Analysis

For continuous variables, parametric analyses were performed using Student's t test, and Mann–Whitney U test was used for non-parametric analyses. Categorical variables and postoperative courses were compared using χ^2 tests with Yates correction. The Kaplan–Meier method was used for analyses of overall survival and disease-free survival, whereas comparisons between groups were performed using the log-rank test. For factors determined to be significant for overall and disease-free survival using univariate analysis, we performed multivariate analyses using the Cox proportional hazards model. An initial Cox proportional hazards model was applied to the entire study population to identify poor prognostic predictors. To overcome bias due to the different distribution of covariates among patients from the 2 groups, a one-to-one match was created using propensity score analysis.[17,18] The propensity score represents the probability of each individual patient being assigned to a particular condition in a study given a set of known covariates. Propensity scores are used to reduce selection bias by equating groups on the basis of these covariates and are used to adjust for selection bias in observational studies through matching. Variables entered in the propensity model were age, sex, anti-hepatitis C virus (HCV) antibody, and liver function test including total bilirubin, prothrombin time, ICG-R15 %, albumin, and Child–Pugh classification. Tumor size, number of tumor, vascular invasion, and AFP were used as tumor factors. Operative bleeding, operative time, transfusion, and type of hepatectomy were used as operative factors. The model was then used to obtain a one-to-one match by using the nearest-neighbor matching method.[19,20] Once the matched groups were obtained, overall and disease-free survival analyses were performed within each matched subgroup to assess the influence of preoperative ATIII level on prognosis after adjusting the confounding factors. A difference was considered significant if the P value was <0.05. Statistical analyses were performed using the SPSS statistical software version 16 (Chicago, Illinois, USA).

RESULTS

ROC Curve Analysis for Cutoff Value of ATIII

The optimal cutoff values of ATIII for survival and recurrence were determined by ROC curve analysis, respectively. A cutoff value of survival was 72 % of ATIII

with a sensitivity of 47 % and specificity of 72 %. A cutoff value of recurrence was 69 % of ATIII with a sensitivity of 36 % and specificity of 81 %. ATIII value of 70 % has been chosen as a cutoff level in this study, since normal ATIII is defined as a level of ≥70 % (Supplementary Figs. 1 and 2).

Clinicopathological Characteristics and Postoperative Course of the Entire Study Group

Differences between the characteristics of patients in the 2 groups are shown in Table 1. Specifically, patients in group 1 had higher prothrombin time (PT) activity, lower serum bilirubin, lower ICG-R15, lower proportion of patients with Child–Pugh class B, greater maximum tumor diameter, and higher frequency of microvascular invasion. The level of preoperative ATIII in group 1 was significantly higher than that in group 2 (88.4 vs. 59.6 %; $P < 0.001$).

In the entire study population, the overall survival rate of patients in group 1 was significantly higher than that of patients in group 2 ($P < 0.001$): in group 1, the 3- and 5-year overall survival rates were 85.0 and 75.8 %, respectively, whereas in group 2, they were 77.1 and 53.1 %, respectively (Fig. 1a). Furthermore, the disease-free survival rate of patients in group 1 was significantly higher than that of patients in group 2 ($P < 0.001$): the 1-, 2-, and 3-year disease-free survival rates were 75.3, 60.1, and 48.1 %, respectively, in group 1 and 63.5, 43.6, and 27.4 %, respectively, in group 2 (Fig. 1b). Postoperative complications did not differ between the 2 groups (Table 2). Table 2 shows the patterns of cancer recurrence and the treatment details of the recurrences in both groups. The overall recurrence rate was also significantly lower in group 1 than in group 2 ($P < 0.001$): 53.5 versus 70.6 %. Regarding treatment for HCC recurrence, the proportion of patients in whom repeat hepatectomy was selected for treatment in group 1 tended to be higher than that in group 2 ($P = 0.07$). Furthermore, the proportion of patients in whom living donor liver transplantation was selected for treatment in group 1 was significantly lower than that in group 2 ($P = 0.038$).

Results after Propensity Score Match

The characteristics of propensity score-matched patients are shown in Table 1. Sixty-five of the 314 patients with preoperative ATIII levels ≥70 % were matched with 65 of the 126 patients with preoperative ATIII levels <70 % after covariate adjustment. Therefore, 249 patients in group 1 and 61 patients in group 2 were excluded because their propensity scores could not be matched. The study group of 130

TABLE 1 Baseline characteristics and operative data on patients who underwent hepatectomy

Characteristic	Whole study series			Propensity matched series		
	ATIII ≥ 70 % ($n = 314$)	ATIII < 70 % ($n = 126$)	*P*	ATIII ≥ 70 % ($n = 65$)	ATIII < 70 % ($n = 65$)	*P*
ATIII (U/ml)	88.4 ± 13.2	59.6 ± 8.5		82.5 ± 11.2	62.3 ± 6.0	
Age (years)	65.2 ± 10.3	64.6 ± 9.4	0.578	65.2 ± 8.2	64.5 ± 10.1	0.685
Sex (M/F)	238/76	85/41	0.074	44/21	42/23	0.711
Anti-HCV antibody positive	185 (59.2 %)	93 (70.8 %)	0.004	47 (72.3 %)	45 (69.2 %)	0.699
Prothrombin time (%)	90.7 ± 16.1	79.1 ± 15.1	<0.001	85.6 ± 14.1	83.8 ± 11.6	0.424
T-Bil (mg/dl)	0.78 ± 0.31	0.91 ± 0.34	<0.001	0.82 ± 0.29	0.83 ± 0.29	0.831
Albumin (g/dl)	4.00 ± 0.42	3.50 ± 0.45	<0.001	3.72 ± 0.36	3.72 ± 0.33	0.939
ICG-R15 (%)	14.8 ± 8.5	23.6 ± 9.7	<0.001	18.4 ± 10.6	18.5 ± 6.8	0.958
Child–Pugh grade, A/B	303/11	96/30	<0.001	60/5	62/3	0.465
Extent of hepatic resection, major/minor	54/260	13/113	0.069	9/56	8/57	0.794
Operation time (min)	292.8 ± 101.8	283.5 ± 105.1	0.394	277.0 ± 84.3	273.9 ± 76.5	0.585
Blood loss (ml)	380.8 ± 478.4	466.8 ± 633.9	0.123	357.5 ± 415.1	357.8 ± 257.8	0.498
Transfusion	18 (5.7 %)	13 (10.3 %)	0.089	2 (3 %)	2 (3 %)	1
AFP (ng/ml)	4568.3 ± 34234	856.3 ± 3546	0.225	884.7 ± 4657	410.8 ± 994.4	0.788
No. of tumors	1.75 ± 1.88	1.62 ± 0.92	0.44	1.65 ± 1.46	1.63 ± 0.91	0.529
Maximum tumor diameter (mm)	39.7 ± 31.4	32.4 ± 27.7	0.024	33.1 ± 23.3	34.0 ± 24.4	0.407
Vascular invasion	94 (29.9 %)	27 (21.4 %)	0.071	16 (24.6 %)	17 (26.1 %)	0.84

Data are reported for whole study and for the matched study population after propensity score analysis. Continuous variables are expressed as mean ± standard deviation

ATIII anti-thrombin III, *HCV* hepatitis C virus, *T-Bil* total bilirubin, *ICG-R15* indocyanine green retention rate at 15 min, *AFP* alfa-fetoprotein

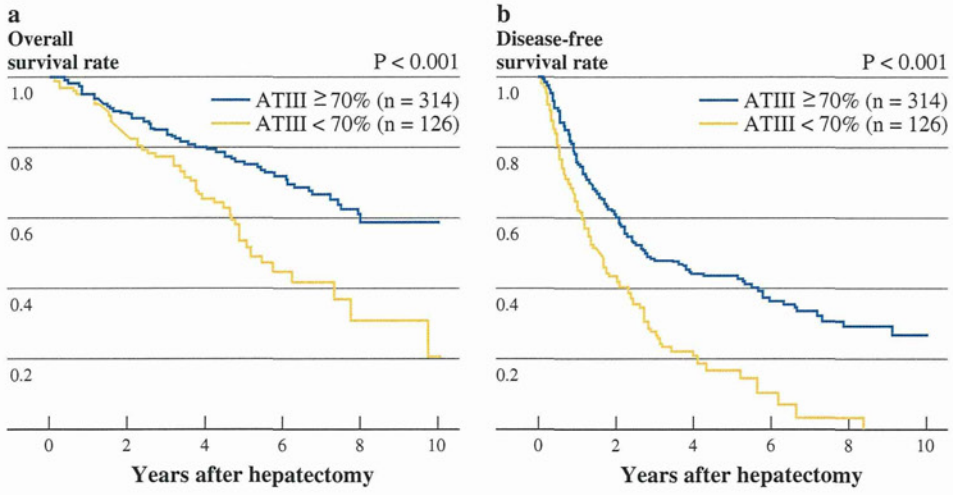

FIG. 1 Outcomes of the entire study population of 440 patients who underwent liver resection for HCC by stratified with the level of ATIII. **a** Kaplan–Meier curves for the overall survival rate after hepatectomy. Overall survival rates of HCC patients with serum ATIII level of more than 70 IU/ml (group 1, $n = 314$) at 3 and 5 years (85.0 and 75.8 %, respectively) were significantly lower than those of the serum ATIII level of <70 IU/ml (group 2, $n = 126$) at 3 and 5 years (77.1 and 53.1 %, respectively) ($P < 0.001$). **b** Kaplan–Meier curves for the disease-free survival rate after hepatectomy. Disease-free survival rates of group 1 at 1, 2, and 3 years (75.3, 60.1, and 48.1 %) were significantly lower than those of the group 2 at 1, 2, and 3 years (63.5, 43.6, and 27.4 %) ($P < 0.001$)

patients was well matched. In particular, all covariates that significantly affected overall survival in the entire study group were equally distributed over the 2 matched groups. Matched patients in groups 1 and 2 had similar anti-HCV antibody positivity (72.3 vs. 69.2 %; $P = 0.699$), PT activity (85.6 vs. 83.8 %; $P = 0.424$), ICG-R15 (18.4 vs. 18.5 %; $P = 0.958$), serum AFP levels (884.7 vs. 410.8 ng/ml; $P = 0.778$), maximum tumor diameter (33.1 vs. 34.0 mm; $P = 0.407$), number of tumors (1.65 vs. 1.63; $P = 0.529$), and microvascular invasion (24.6 vs. 26.1 %; $P = 0.840$). Other clinical variables and tumor characteristics were also similar in both groups. The preoperative ATIII level of patients in group 1 was significantly higher than that of patients in group 2 (82.5 vs. 62.3 %; $P < 0.001$). The postoperative course of the matched study groups is shown in Table 2. Postoperative complications did not differ between the 2 groups. The mean follow-up period ± standard deviation of groups 1 and 2 was 37.8 ± 36.2 and 34.3 ± 31.0 months, respectively. The overall survival rate of patients in group 1 was significantly higher than that of patients in group 2 ($P = 0.005$): in group 1, the 3-, and 5-year overall survival rates were 92.5 and 83.4 % respectively, whereas in group 2, they were 75.8 and 57.1 %, respectively (Fig. 2a). Furthermore, the disease-free survival rate of patients in group 1 was significantly higher than that of patients in group 2 ($P = 0.012$): the 1-, 2-, and 3-year disease-free survival rates were 74.3, 52.6, and 37.0 %, respectively, in group 1 and 55.6, 43.0, and 29.1 %, respectively, in group 2 (Fig. 2b).

Table 2 shows the patterns of cancer recurrence and the treatment details of the recurrences in both groups. The overall recurrence rate in group 1 tended to be lower than that of group 2 (58.5 vs. 73.8 %; $P = 0.064$). Regarding treatment for HCC recurrence, the proportion of patients in whom repeat hepatectomy was selected for treatment in group 1 tended to be higher than that in group 2 ($P = 0.093$). Furthermore, the proportion of patients in whom TACE was selected for treatment in group 1 was significantly lower than that in group 2 ($P = 0.041$).

Table 3 shows the results from the univariate and multivariate analyses of prognostic factors for overall survival in the whole study. Factors found to be significant in the univariate analysis were PT activity, serum ATIII level, serum albumin level, Child–Pugh grade, extension of hepatectomy, operation time, transfusion, serum AFP level, multiple tumors, tumor size, and microscopic vascular invasion. Multivariate analysis revealed that PT activity, serum ATIII level, serum AFP level, multiple tumors, and microscopic vascular invasion were the independent prognostic factors of overall survival. Table 4 shows the results from the univariate and multivariate analyses of prognostic factors for disease-free survival in the whole study. Factors found to be significant in the univariate analysis include HCV antibody, PT activity, serum ATIII level, serum total bilirubin level, serum albumin level, ICG-R15, Child–Pugh grade, operation time, serum AFP level, multiple tumors, and microscopic vascular invasion. Multivariate analysis revealed that PT activity, serum

TABLE 2 Follow-up data including postoperative complications after curative hepatectomy

Characteristic	Whole study series			Propensity matched series		
	ATIII (≥70 U/ml) (n = 314)	ATIII (<70 U/ml) (n = 126)	P	ATIII (≥70 U/ml) (n = 65)	ATIII (<70 U/ml) (n = 65)	P
Mean follow-up duration (years)	4.09 ± 2.87	3.55 ± 2.30		4.3 ± 2.56	3.46 ± 2.21	
Operative complications						
Clavien–Dindo grade[a]			0.3			1
IIIa	12 (3.8 %)	6 (4.8 %)		2	2	
IIIb	4 (1.3 %)	2 (1.6 %)		0	0	
IVa	0	2 (1.6 %)		0	0	
IVb	2 (0.6 %)	0		0	0	
V	1 (0.3 %)	1 (0.8 %)		0	0	
90-day mortality	10 (3.2 %)	5 (4.0 %)	0.68	2 (3.1 %)	4 (6.2 %)	0.4
Overall recurrence	168 (53.5 %)	89 (70.6 %)	<0.001	38 (58.5 %)	48 (73.8 %)	0.064
First recurrence time (years)	1.83 ± 1.76	1.59 ± 1.57	0.28	1.63 ± 1.40	1.43 ± 1.46	0.52
Recurrence pattern[a]						
Intrahepatic	130 (41.4 %)	81 (64.3 %)	<0.001	34 (52.3 %)	44 (67.7 %)	0.073
Single	58 (18.5 %)	40 (31.7 %)	0.002	14 (21.5 %)	23 (35.4 %)	0.08
Multiple	72 (22.9 %)	41 (32.5 %)	0.037	20 (30.8 %)	21 (32.3 %)	0.85
Extrahepatic	38 (12.1 %)	8 (6.3 %)	0.075	4 (6.2 %)	4 (6.2 %)	1
Main treatment for first recurrence[b]						
Hepatectomy	43 (25.6 %)	14 (15.7 %)	0.07	16 (42.1 %)	12 (25.0 %)	0.093
RFA	28 (16.7 %)	20 (22.5 %)	0.256	7(18.4 %)	10 (20.8 %)	0.78
PEI	7 (4.2 %)	3 (3.4 %)	0.754	4 (10.5 %)	3 (6.3 %)	0.471
TACE	55 (32.7 %)	36 (40.4 %)	0.546	6 (15.8 %)	17 (35.4 %)	0.041
LDLT	2 (1.2 %)	5 (5.6 %)	0.038	1 (2.6 %)	1 (2.1 %)	0.867
Other	22 (13.1 %)	5 (5.6 %)	0.063	1 (2.6 %)	3 (6.3 %)	0.429
No treatment	11 (6.5 %)	6 (6.7 %)	0.953	0	2 (4.2 %)	0.203

ATIII serum antithrombin III, *RFA* radiofrequency ablation, *PEI* percutaneous ethanol injection, *TACE* transcatheter arterial chemoembolization, *LDLT* living donor liver transplantation

[a] Data are expressed as the number of patients (percentage of total patients)

[b] Data are expressed as the number of patients (percentage of patients with recurrence)

ATIII level, serum AFP level, multiple tumors, and microscopic vascular invasion were the independent prognostic factors of overall survival.

DISCUSSION

To our knowledge, this is the first study that investigates the influence of ATIII on HCC patients using propensity score analysis. The present study demonstrated that when other prognostic variables were appropriately adjusted for, overall and disease-free survival after hepatectomy was significantly prolonged in HCC patients with high preoperative levels of ATIII. Therefore, a low preoperative level of ATIII may be considered a risk factor for tumor recurrence and prognosis. The results of this study are in agreement with certain studies, which showed that a decrease in plasma ATIII levels was a risk factor for tumor recurrence and prognosis in patients with several cancers including lung, colon, ovary, and prostate cancers.[6–8]

The serpin ATIII controls a number of important coagulation enzymes, including factor Xa and thrombin, with the aid of its cofactor, heparin. Heparin activates antithrombin by inducing conformational changes in the protein that specifically enhances binding. While the classical function of ATIII is of an anticoagulant regulator of blood clotting proteinases such as thrombin, recent studies demonstrate its ability to attenuate inflammatory responses by inhibiting cytokines and other inflammatory mediators found within serum and tissue.[3] ATIII has also been reported to suppress the invasion and metastasis of several cancers. Recent studies by Kurata et al.[21] indicate that ATIII prevented hepatic ischemia/reperfusion-induced metastasis of colon cancer cells in a rat model by blocking tumor necrosis factor alpha production. Macrophage inhibitory factor (MIF) has been known to be associated

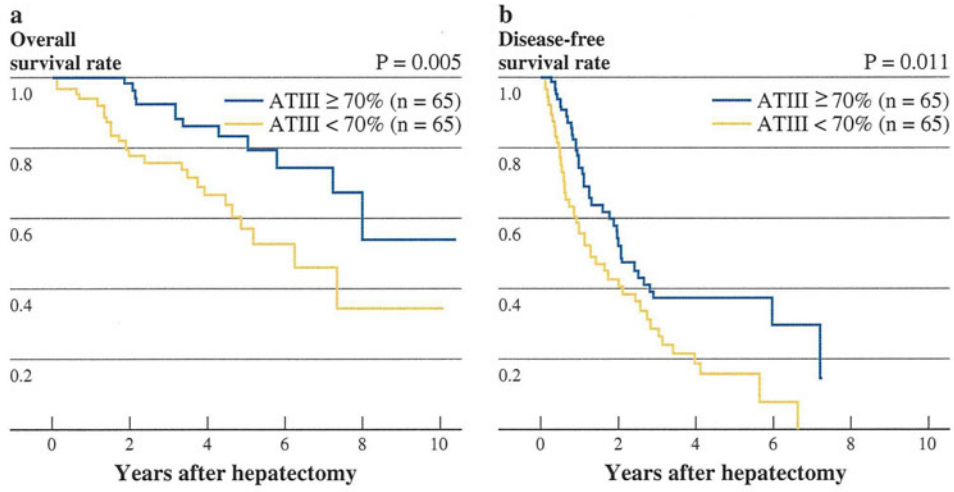

FIG. 2 Outcomes of the matched study population of 130 patients who received liver resection for HCC by stratified with the level of ATIII. **a** Kaplan–Meier curves for the overall survival rate after hepatectomy. Overall survival rates of HCC patients with serum ATIII level of >70 IU/ml (group 1, $n = 65$) at 3 and 5 years (92.5 and 83.4 %, respectively) were significantly lower than those of the serum ATIII level of <70 IU/ml (group 2, $n = 65$) at 3 and 5 years (75.8 and 57.1 %, respectively) ($P = 0.005$). **b** Kaplan–Meier curves for the disease-free survival rate after hepatectomy. Disease-free survival rates of group 1 at 1, 2, and 3 years (74.3, 52.6, and 37.0 %) were significantly lower than those of the group 2 at 1, 2, and 3 years (55.6, 43.0, and 29.1 %) ($P = 0.012$)

with some cancer cell proliferation and invasion. ATIII has been identified as an endogenous MIF-binding protein by forming ATIII–MIF complexes, which reduces MIF biological activity.[22] Recent evidence has shown that thrombin contributes to a more malignant phenotype in vivo by activating tumor-platelet adhesion, tumor adhesion to the subendothelial matrix, tumor implantation, tumor growth, and tumor-associated angiogenesis.[23–25] Kaufmann et al.[26] have shown that some HCC cell lines express a thrombin receptor, proteinase-activated receptor (PAR), and a thrombin-induced increase in HCC cell migration by mediating PAR. Rullier et al.[27] have shown that PAR-1 positive tumor cells are found in HCC. These results suggest that ATIII can suppress proliferation and migration of HCC cells by inhibiting thrombin-induced tumor growth and angiogenesis. It has been also shown that the expression of osteopontin is increased significantly in HCC, and is closely associated with poor prognosis, early recurrence, and metastasis.[28,29] Thrombin cleaves osteopontin into 2 fragments of approximately equivalent size. Osteopontin fragments generated by thrombin cleavage enhance proliferation and adhesion of HCC cells through the activation of integrin β-focal adhesion kinase signaling.[30] Thrombin has been shown to contribute to tumor progression in both a coagulation-dependent and coagulation-independent manner.[31] Further basic and clinical studies are needed to elucidate the antitumor mechanisms of ATIII.

In this study, repeat hepatectomy rather than TACE was selected as a recurrence treatment in more patients with normal level of ATIII, while more patients with decreased level of ATIII underwent TACE rather than hepatectomy for recurrence. This result was thought to be due to high occurrence of early recurrence within 1 year of surgery in patients with decreased level of ATIII. Many cases of recurrence within 1 year after primary hepatectomy are thought to be intrahepatic metastasis from the primary HCC, and survival rate in patients with early recurrence showed worse outcome.[32,33] In our series, most patients who had early recurrence within 1 year of primary hepatectomy were unlikely to receive repeat hepatectomy. Portolani et al.[2] have reported that curative treatment including surgery, percutaneous ethanol injection, and radiofrequency ablation, was feasible in 29.3 % in the early recurrence, while it was 67.6 % in the late recurrence: the proportion of patients who underwent curative treatment for HCC recurrence was significantly higher in the late recurrence than in the early recurrence ($P < 0.05$).

In this study, we have chosen the cutoff for ATIII based on the lower limit of normal level. The optimal cutoff values of ATIII for survival and recurrence determined by ROC curve analysis were 69 and 72 %, respectively. These results indicate that the cutoff value of ATIII with 70 % is valid in this study, and these results are consistent with that normal ATIII is defined as a level of ≥70 %.

Before matching by using the propensity score, the clinical characteristics of the entire study population that can strongly influence outcomes differed significantly between the 2 groups. The proportion of patients with better liver function was higher in group 1 than in group 2, and the proportion of patients with advanced HCC also

TABLE 3 Univariate and multivariate analysis of predictive variables of overall survival in the whole study

Variable	Univariate analysis		Multivariate analysis		
	5-year survival rate (%)	*P*	Hazard ratio	95 % CI	*P*
Age					
≥70 ($n = 167$); <70 ($n = 273$)	68.2; 69.7	0.959			
Gender					
Male ($n = 323$); female ($n = 117$)	69.9; 68.9	0.646			
Anti-HCV antibody					
Positive ($n = 279$); negative ($n = 161$)	68.5; 70.1	0.357			
Prothrombin time (%)					
≥80 ($n = 307$); <80 ($n = 133$)	77.0; 56.7	<0.001	1.62	1.069–2.457	0.023
ATIII (%)					
≥70 ($n = 314$); <70 ($n = 126$)	75.8; 53.1	<0.001	1.596	1.012–2.516	0.044
T-Bil (mg/dl)					
≤1.0 ($n = 307$); >1.0 ($n = 133$)	72.1; 63.0	0.196			
Albumin (g/dl)					
≥4.0 ($n = 332$); <4.0 ($n = 108$)	71.7; 61.7	0.048	1.034	0.621–1.719	0.898
ICG-R15 (%)					
>15 ($n = 213$); ≥15 ($n = 227$)	73.2; 65.6	0.093	1.088	0.729–1.623	0.681
Child–Pugh grade					
A ($n = 399$); B ($n = 41$)	71.9/50.8	0.001	0.792	0.418–1.501	0.475
Extend of hepatic resection					
Major ($n = 373$); minor ($n = 67$)	70.5; 61.2	0.023	0.751	0.449–1.283	0.237
Operation time (h)					
≥6 ($n = 280$); >6 ($n = 180$)	73.2; 62.5	0.008	0.844	0.553–1.289	0.433
Blood loss (ml)					
<1,000 ($n = 34$); ≥1,000 ($n = 406$)	69.9; 60.2	0.065	1.3	0.607–3.402	0.414
Transfusion					
No ($n = 409$); yes ($n = 31$)	71.2; 40.0	<0.001	0.641	0.293–1.296	0.122
AFP (ng/ml)					
≤100 ($n = 313$); >100 ($n = 127$)	76.2; 53.2	<0.001	0.571	0.417–0.924	0.004
No. of tumor					
Single ($n = 286$); multiple ($n = 154$)	77.0; 54.7	<0.001	0.532	0.386–0.824	0.001
Tumor size (5 cm)					
≥5 ($n = 365$); <5 ($n = 75$)	70.8; 62.3	0.033	0.917	0.505–1.664	0.776
Vascular invasion					
No ($n = 319$); yes ($n = 121$)	76.1; 51.8	<0.001	2.05	1.303–2.901	0.0001

HCV hepatitis C virus, *ATIII* anti–thrombin III, *T-Bil* total bilirubin, *ICG-R15* indocyanine green retention rate at 15 min, *AFP* alfa-fetoprotein

tended to be higher in the group 1 than in the group 2. To overcome bias due to the different distribution of the severity of liver function impairment between the 2 groups, a one-to-one match was created using propensity score analysis. After matching by propensity score, prognostic variables were appropriately handled, and there was no significant difference in prognostic factors excluding ATIII between the 2 matched groups. This study had a limitation related to the small sample size after propensity score matching. Two hundred forty-nine patients in group 1 and 61 patients in group 2 were excluded by propensity score matching, because their propensity scores could not be matched. Thus, further examination with a larger number of patients may be necessary.

Multivariate analysis agreed with that in previous publications, showing that vascular invasion, multiple tumors, and tumor marker such as AFP were independent prognostic factors associated with overall and disease-free survival rates. These results were compatible with previous reports.[34,35] Regarding with liver function, PT activity and

TABLE 4 Univariate and multivariate analysis of predictive variables of disease-free survival in the whole study

Variable	Univariate analysis		Multivariate analysis		
	5-year survival rate (%)	*P*	Hazard ratio	95 % CI	*P*
Age					
≥70 (n = 167); <70 (n = 273)	36.4; 39.7	0.377			
Gender					
Male (n = 323); female (n = 117)	36.6; 39.2	0.357			
Anti-HCV antibody					
Positive (n = 279); negative (n = 161)	34.4; 45.9	0.0164	0.728	0.482–1.101	0.133
Prothrombin time (%)					
≥80 (n = 307); <80 (n = 133)	47.5; 20.5	<0.001	1.621	1.074–2.447	0.021
ATIII (%)					
≥70 (n = 314); <70 (n = 126)	45.7; 20.0	<0.001	1.596	1.012–2.516	0.044
T-Bil (mg/dl)					
≤1.0 (n = 307); >1.0 (n = 133)	43.1; 29.1	0.023	1.009	0.677–1.505	0.965
Albumin (g/dl)					
≥4.0 (n = 332); <4.0 (n = 108)	42.3; 27.4	<0.001	1.043	0.630–1.727	0.871
ICG-R15 (%)					
>15 (n = 213); ≥15 (n = 227)	46.9; 30.3	<0.001	1.088	0.729–1.623	0.681
Child–Pugh grade					
A (n = 399); B (n = 41)	40.6; 21.3	0.034	0.518	0.438–1.517	0.518
Extent of hepatic resection					
Major (n = 373); minor (n = 67)	37.5; 43.6	0.349			
Operation time (h)					
≥6 (n = 280); >6 (n = 180)	40.1; 35.8	0.018	0.84	0.559–1.261	0.4
Blood loss (ml)					
<1000 (n = 34); ≥1000 (n = 406)	40.6; 38.4	0.276			
Transfusion					
No (n = 409); yes (n = 31)	41.0; 38.4	0.262			
AFP (ng/ml)					
≤100 (n = 313); >100 (n = 127)	39.4; 27.0	0.004	0.568	0.386–0.836	0.004
No. of tumors					
Single (n = 286); multiple (n = 154)	43.9; 29.1	<0.001	0.555	0.379–0.811	0.002
Tumor size (5 cm)					
≥5 (n = 365); <5 (n = 75)	37.7; 48.0	0.372			
Vascular invasion					
No (n = 319); yes (n = 121)	76.1; 39.2; 28.751.8	0.004	2.031	1.368–3.015	0.0001

HCV hepatitis C virus, *ATIII* anti–thrombin III, *T-Bil* total bilirubin, *ICG-R15* indocyanine green retention rate at 15 minutes, *AFP* alfa-fetoprotein

ATIII level were significant factors in multivariate analysis. Operative variables such as extension of hepatectomy, blood loss, and transfusion, were associated with poor outcomes in univariate analyses, but these factors were not significant factors in the multivariate analysis.

In conclusion, one-to-one matching study using propensity scores and multivariate analysis showed that the ATIII level was associated with favorable outcomes in HCC patients after curative hepatectomy. ATIII may be useful for predicting outcomes of patients with HCC after curative hepatectomy.

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Safety and Feasibility of Diet-Treated Donors With Steatotic Livers at the Initial Consultation for Living-Donor Liver Transplantation

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Background. The purpose of this study was to evaluate both safety of diet-treated donors and the feasibility of their use for living-donor liver transplantation (LDLT).

Methods. A total of 128 living donors were enrolled in this study between April 2003 and March 2010. Of them, 41 were diagnosed with hepatic steatosis at the initial consultation. Donor selection was based on the findings of liver biopsy accompanied with normalization of liver function tests after diet treatment consisting of an 800 to 1400 kcal/day diet and a 100 to 400 kcal/day exercise without drug treatment, targeting body mass index of 22 kg/m^2.

Results. Body mass index of diet-treated donors was significantly reduced with diet from 23.3±0.6 to 21.9±0.4 kg/m^2 (P<0.0001). Liver function tests associated with fatty liver, including alanine aminotransferase, gamma-glutamyl transpeptidase, and total cholesterol levels, also improved with diet (P=0.0128, 0.0016, and 0.0004, respectively). The liver biopsy results of most of these donors showed stage 0/1 fibrosis and minimal/mild steatosis after the diet therapy. Surgical outcomes, including postoperative liver function tests, perioperative complications, and liver regeneration rates, did not significantly differ between nondiet-treated and diet-treated donors. Surgical outcomes and the overall survival did not significantly differ between recipients of grafts from nondiet-treated and diet-treated donors.

Conclusion. The use of diet-treated donors for living-donor liver transplantation is feasible with respect to donor safety and the outcome of the recipient when strict selection criteria are used.

Keywords: Diet, Steatosis, Living donor liver transplantation, Biopsy, Fatty liver.

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Liver transplantation is the only treatment option for patients with end-stage liver disease. However, the shortage of organs remains a serious problem, and annual death rates per 1000 patient-years at risk is 113.6 while on the waiting list (United Network for Organ Sharing at www.unos.org. accessed in May 2009). Many liver transplantation centers have been forced to modify their criteria for acceptable donors to increase the donor pool. A modified extended criteria donor has been applied to deceased-donor liver transplantation (DDLT), including older donors, donors with prolonged ischemia, donation after cardiac death, those with liver infected with certain viruses, obese donors, and those with steatotic (fatty) livers (*1*).

Implantation of donor livers with severe fatty infiltration is frequently associated with a high incidence of severe ischemic damage, resulting in primary dysfunction and/or primary nonfunction after DDLT (*2–6*).

Meanwhile, living-donor liver transplantation (LDLT) has been accepted and established as an alternative to DDLT (*7*) since it was first successfully performed in 1989 (*8*). Soejima et al. (*9*) described the feasibility of using a steatotic graft even in LDLT with respect to primary nonfunction and reported the effectiveness of short-term treatments consisting of a protein-rich diet, exercise, and bezafibrate for 2 to 8 weeks for donors with a fatty liver (*10*). The obvious advantages of LDLT are the reduction in the mortality of patients on the transplant waiting list and the provision of sufficient preparation time, which is a great merit in scheduling the transplantation (*11*, *12*). In our institute, a candidate of living donors with a fatty liver at the initial

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TABLE 1. Effects of diet on donors

	Nondiet treated (N=87)		Diet treated (N=41)		
		P	Initial consultation	*P*	Postdiet
BMI (kg/m^2)	21.8±0.3	0.0163	23.3±0.6	< 0.0001	21.9±0.4
T. Bil (mg/dL)	0.9±0.0	0.2870	0.8±0.1	0.2556	0.8±0.1
D. Bil (mg/dL)	0.1±0.0	0.3256	0.1±0.1	0.2323	0.1±0.1
AST (IU/L)	18±1	0.0016	22±1	0.1042	20±1
ALT (IU/L)	18±1	0.0007	28±3	0.0128	21±1
γ-GTP (IU/L)	24±2	0.0003	41±6	0.0016	28±4
PT-INR	0.98±0.01	0.1006	0.96±0.01	0.0435	0.98±0.01
Alb (g/dL)	4.8±0.0	0.9389	4.8±0.1	0.0074	4.7±0.1
T-cho (mg/dL)	186±4	0.0002	213±6	0.0004	173±9
TG (mg/dL)	80±5	0.0021	110±9	0.6506	108±13

Continuous variables are expressed as means±standard error.

BMI, body mass index; T. Bil, total bilirubin; D. Bil, direct bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, gamma-glutamyl transpeptidase; PT-INR, prothrombin time-international normalized ratio; Alb, albumin; T-cho, total cholesterol; TG, triglyceride.

consultation in the outpatient clinic is examined for his or her potential as a donor after administering a diet treatment. Herein, we refer to these donors as "diet-treated donors." Few studies have analyzed the outcomes of LDLT using diet-treated donors with steatotic livers (*13*).

The aim of this study was to evaluate both safety of the donors and the outcomes of the recipients undergoing LDLT from diet-treated donors.

RESULTS

Effects of Diet on Donors

A total of 87 donors did not receive diet treatment (nondiet-treated donors), and 41 donors were treated with a diet (diet-treated donors). The mean body mass index (BMI) and the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (γ-GTP), total cholesterol (T-cho), and triglyceride (TG) were significantly higher in diet-treated donors at the initial consultation than in nondiet-treated donors. After the diet, BMI was significantly reduced from 23.3±0.6 to 21.9±0.4 kg/m^2 (P<0.0001) for a median period of 2.9 (range, 0.2–13.6) months, which was limited by the critical status of the recipients. Factors associated with hepatic steatosis, including ALT, γ-GTP, and T-cho levels, also improved with the diet treatment (P=0.0128, 0.0016, and 0.0004, respectively), whereas the level of albumin decreased significantly (P=0.0074) (Table 1).

The results of the preoperative liver biopsy are presented in Table 2. In most of the diet-treated donors, a liver biopsy performed after the diet showed stage 0/1 fibrosis and minimal or mild steatosis. One diet-treated donor had stage 2 perisinusoidal/pericellular fibrosis and a minimal grade of macrovesicular steatosis. No complications associated with liver biopsy were reported.

Preoperative Characteristics of Donors and Recipients

The diet-treated donors were significantly older than the nondiet-treated donors (40.2±1.6 years vs. 35.5±1.4 years, P=0.0484). The mean values of BMI, total bilirubin (T. Bil), AST, ALT, and prothrombin time-international normalized ratio (PT-INR) of the donors measured just before the operation were comparable between the two groups. Although the model for end-stage liver disease (MELD) score was not significantly different between the two groups, it was likely to be higher in the recipients of grafts from nondiet-treated donors than in those of grafts from diet-treated donors (18.1±0.9 vs. 15.2±1.1, P=0.0552) (Table 3). In those of grafts from diet-treated donors, mean MELD score was increased from 13.3 to 15.2 during the diet period.

Surgical Demographics of Donors and Recipients

There were no significant differences between the two groups with respect to graft type and surgical data of donors and recipients, including operative time, blood loss, blood transfusions, graft-to-recipient weight ratio, and cold ischemic time (Table 4).

Donor Postoperative Data

There were no significant differences in perioperative laboratory data on T. Bil, AST, and ALT. Just PT-INRs on postoperative days 1, 2, and 3 were significantly higher in nondiet-treated donors than in diet-treated donors. However, there were no significant differences after postoperative day 5 (Fig. 1). Perioperative complications categorized according to the Clavien's grading system (*14*) showed no

TABLE 2. Results of the liver biopsy

	Stage				
Grade	0	1	2	3	4
Minimal	9	29	1	0	0
Mild	0	2	0	0	0
Moderate	0	0	0	0	0
Severe	0	0	0	0	0

Minimal, ≤10%; mild, 11%–20%; moderate, 21%–30%; severe, >30%.

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TABLE 3. Preoperative demographics of donors and recipients

	Nondiet treated (N=87)	Diet treated (N=41)	*p*
Donor			
Age	35.5±1.4	40.2±1.6	0.0484
Gender			
Male	52	27	0.5088
Female	35	14	
Body weight (kg)	59.5±1.1	60.1±1.4	0.7191
BMI (kg/m^2)	21.8±0.3	21.9±0.4	0.7657
Liver function test			
T. Bil (mg/dL)	0.9±0.0	0.8±0.1	0.6782
AST (IU/L)	18±1	20±1	0.1212
ALT (IU/L)	18±1	21±1	0.1088
PT-INR	0.98±0.01	0.98±0.01	0.6924
Relation to the recipient			
Child	50	22	0.2146
Spouse	14	11	
Sibling	11	7	
Parent	8	1	
Others (son in law, niece, and nephew)	4	0	
Recipient			
Age	52.5±1.1	52.8±1.5	0.8715
Gender			
Male	54	26	0.8833
Female	33	15	
Body weight (kg)	63.5±1.3	64.3±2.0	0.7253
Indications			
HCC	37	23	
LC due to HCV	17	5	
FHF	7	1	
LC due to alcohol abuse	4	3	
LC due to HBV	4	2	
Secondary biliary cirrhosis	4	0	
PBC	3	3	
PSC	3	0	
AIH	3	1	
Wilson disease	1	1	
Liver failure posthepatectomy	1	1	
NASH	1	0	
Metastatic liver tumor (insulinoma)	1	0	
Retransplantation	1	0	
Budd-chiari syndrome	0	1	
MELD score	18.1±0.9	15.2±1.1	0.0552
ABO incompatibility			
Identical/compatible	80	35	0.2496
Incompatible	7	6	

Continuous variables are expressed as means±standard error.

BMI, body mass index; T. Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PT-INR, prothrombin time-international normalized ratio; HCC, hepatocellular carcinoma; LC, liver cirrhosis; HCV, hepatitis C virus; FHF, fulminant hepatic failure; HBV, hepatitis B virus; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; AIH, autoimmune hepatitis; NASH, nonalcoholic steatohepatitis; MELD, Model for End-Stage Liver Disease.

significant differences between the two groups. Perioperative complications in patients with a Clavien grade III or higher included an intraabdominal hematoma in one nondiet-treated donor, biliary leakages in two nondiet-treated donors, and a biliary stenosis in one diet-treated donor. For the right lobe graft, liver regeneration rates on postoperative day 7 were 1.41±0.03 in nondiet-treated donors and 1.44±0.04 in diet-treated donors (P=0.574). For the remaining grafts,

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liver regeneration rates were also comparable between the two groups.

Overall Survival in Recipients

There were no significant differences in overall survival between recipients of grafts from nondiet-treated and diet-treated donors. The 1-, 3-, and 5-year survival rates were 79%, 74%, and 70% for recipients of grafts from nondiet-treated donors, whereas the corresponding values were 68%, 68%, and 68% for recipients of grafts from diet-treated donors, respectively (P=0.455).

Biliary Complications in Recipients

Biliary complications in the recipients, including stricture, leakage, and stricture after leakage, showed no statistically significant differences between nondiet-treated and diet-treated donors. The number of patients with biliary diversion was also comparable (data not shown).

DISCUSSION

The condition of both donors and recipients is a critical issue in LDLT. Although safety of donors should be of the highest priority (*15*, *16*), there is considerable controversy with respect to that of extended criteria donors. In particular, it has not been well elucidated if fatty liver affects the donor safety, whereas steatotic liver grafts have been well analyzed and there is still controversy regarding the outcome of recipients (*4–6*).

The incidence of obesity has increased dramatically in developed countries in the last few decades. There has also been a simultaneous rise in the frequency of metabolic syndrome. Nonalcoholic fatty liver disease is characterized by an elevated intrahepatic TG content, with varying degrees of inflammation and fibrosis. A clear differentiation between a simple fatty liver and nonalcoholic fatty liver disease is difficult in the absence of liver biopsy results. Macrovesicular steatosis can lead to inflammation and fibrosis, and the likelihood of graft damage in recipients of a liver graft from a donor with macrovesicular steatosis is high (*17*, *18*). Therefore, the criteria of fatty liver were widened in this study. They were based only on the imaging studies including computed tomography (CT) and/or ultrasound. Oliva et al. (*19*) reported that liver-spleen ratio of less than 1.2 covered all the cases with fatty liver, whereas some authors underlined 1.0 or 1.1 as the cutoff line for fatty liver (*20*, *21*). The authors followed the criteria of Oliva et al. Ruhl and Everhart (*22*) reported that the proportion of elevated ALT activity due to excess weight and obesity (BMI>25 kg/m^2) was 65%. Rinella et al. (*23*) reported a significant correlation between BMI and the degree of macrovesicular steatosis and found that patients with a BMI of less than 25 kg/m^2 did not show macrovesicular steatosis. Moreover, Peng et al. (*24*) reported that patients with a BMI of less than 23 kg/m^2 were likely to display no or mild steatosis. Consequently, the target BMI value in this study was set to 22 kg/m^2. In this study, the results of liver function tests related to hepatic steatosis were significantly improved after the diet treatment. In addition, the histopathological results of the liver biopsies performed after the diet treatment showed less than 20% of macrovesicular steatosis. The main objective of the liver biopsy is to ensure donor safety, which is considered more important than the preservation of graft function (*25*).

TABLE 4. Surgical demographics of donors and recipients

	Nondiet treated (N=87)	Diet treated (N=41)	p
Donor			
Graft type			
Right lobe without MHV	68	29	0.4509
Left lobe with MHV	17	10	
Left lobe without MHV	1	0	
Posterior section	1	2	
Operative time (min)	408±7	409±10	0.9253
Blood loss (mL)	227±15	241±35	0.6772
Allogenic blood transfusion	0	0	
Autologous blood transfusion			
Yes	6	5	0.3183
No	81	36	
Recipient			
Operative time (min)	725±14	752±17	0.2417
Blood loss (mL)	4153±272	4566±612	0.4755
PRBC (U)	7.6±0.8	8.4±1.6	0.6323
FFP (U)	6.6±0.9	5.7±1.2	0.5765
GW (g)	581±14	609±26	0.3109
GRWR (%)	0.94±0.02	0.96±0.05	0.6632
CIT (min)	98±4	100±5	0.7346

Continuous variables are expressed as means±standard error.

MHV, middle hepatic vein; PRBC, packed red blood cell; FFP, fresh-frozen plasma; GW, graft weight; GRWR, graft-to-recipient weight ratio; CIT, cold ischemic time.

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