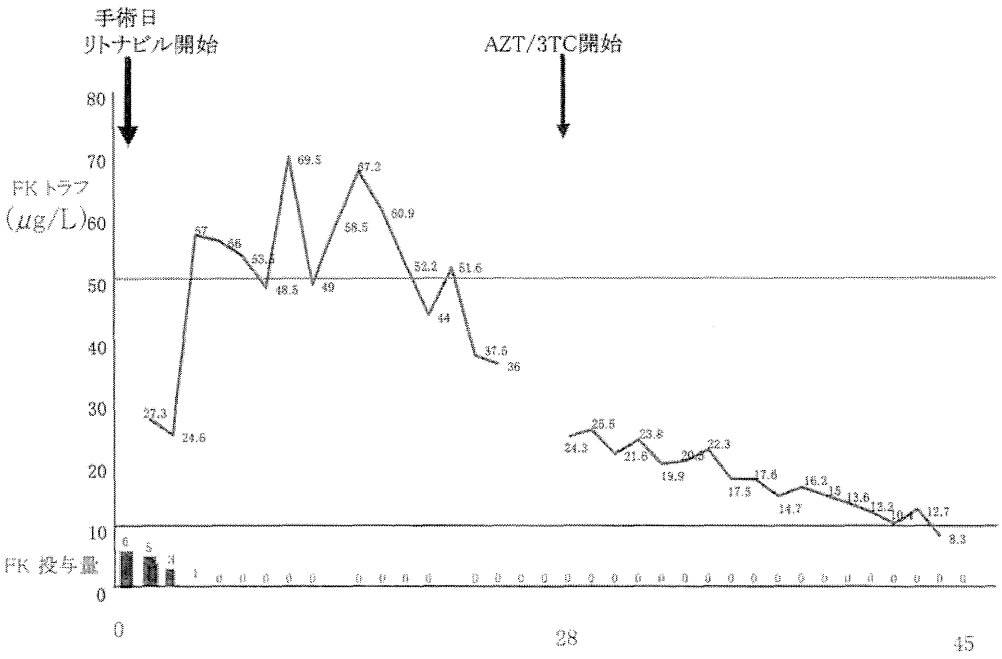

図 3 (1)　術後 FK506 血中濃度の推移

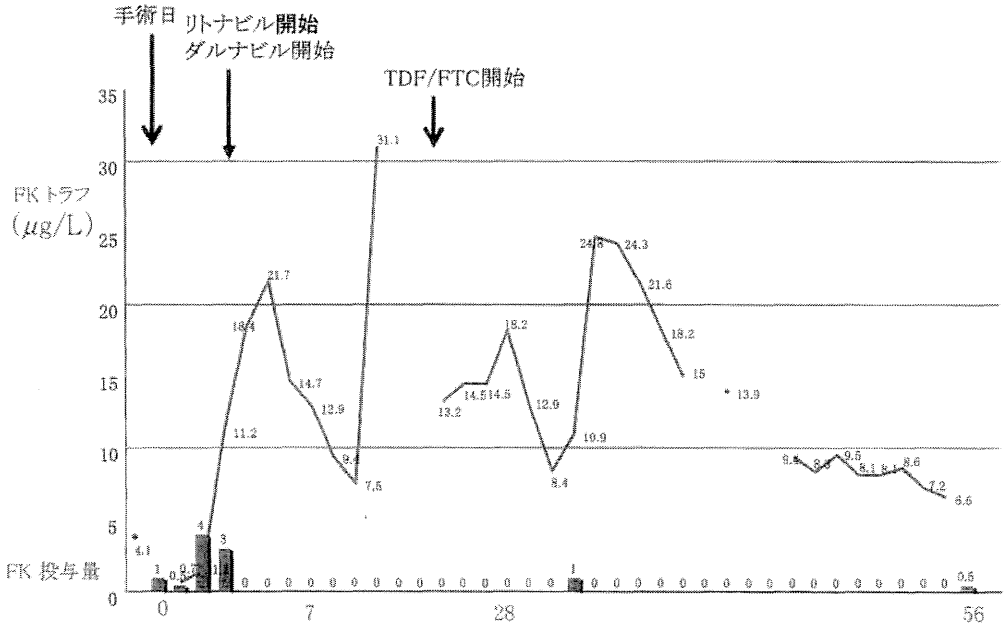

図 3 (2)　術後 FK506 血中濃度の推移

染患者では ACTIVE な感染症がないことが適応条件である。一般的には，CD4 200/μL 以上，HIV のウイルスが感知されないことが，肝移植適応条件となるが，最近ではマイアミ大学では，あまり CD4 陽性 T 細胞の数にこだわっていないのが現状である。CD4 陽性 T 細胞の実数は中央値 155 (23～1,045) で，CD4 陽性 T 細胞の % は 26% (8～50%) であった。これは肝硬変の患者では総白血球数，総リンパ球数が減少しており，それ自体が肝移植成績とは関連しないと考えたからである。厚生労働研究小池班のガイドラインでは，CD4 陽性 T 細胞実数が 250 以上を適応としている[10] が，今回のマイアミでのデータに基づき，高度肝硬変の患者では CD4 陽性 T 細胞の移植基準値をたと

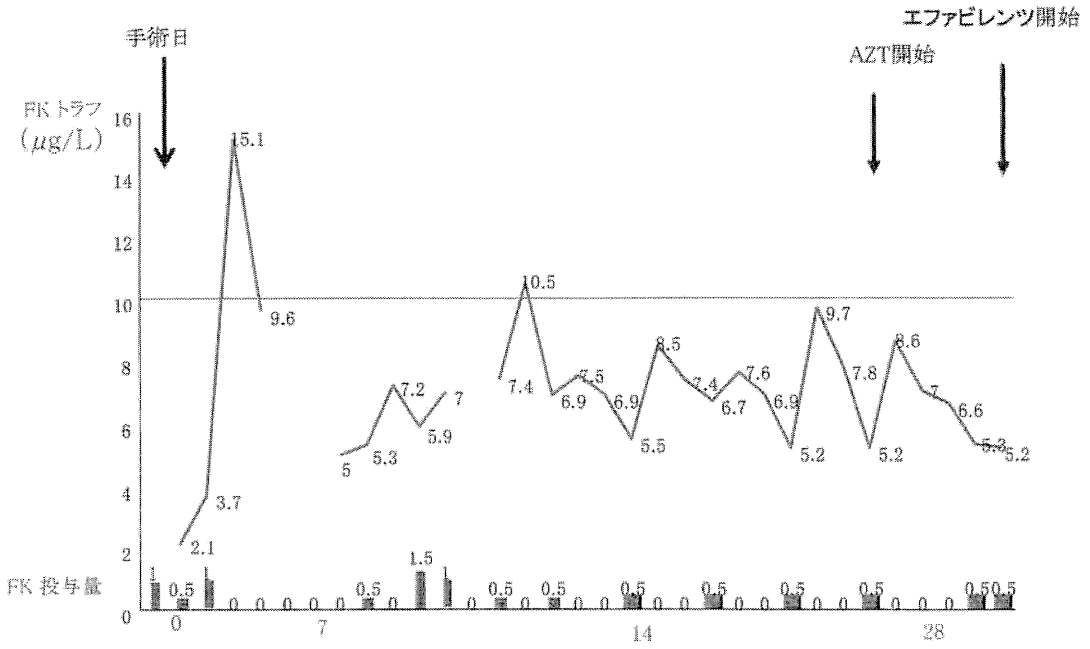

図 3 (3) 術後 FK506 血中濃度の推移

えば 150 などに低下させてもよい可能性が示唆される。また，脾臓摘出術を併施することを計画しているさいは，術後 CD4 陽性 T 細胞数の上昇も予想される。移植後の感染性合併症も特に上昇しておらず，マイアミ大学のように通常の肝移植管理＋HIV 感染症内科また血友病患者では血液内科の合同チームにより multi-disciplinary team を形成し，肝移植の成功率の向上に寄与しうると考えられた。

HIV 陽性感染者に対する肝移植で通常の肝移植と異なる問題点は次のような事項があげられる。1. HAART との併用によるカルシニューリン阻害薬の著明な血中濃度上昇[11]，2. 適正な HAART 開始のタイミングが未確立で，早期開始での薬剤性肝障害のリスク高[12]，3. HAART 開始の遅れによる日和見感染のリスク，4. HIV 陽性患者に対して移植の考慮が遅れ，結果として移植時期が遅れる，5. HCV 重複感染例では，HIV のみ陽性患者に比較して，HCV 再発後の進展が早い[13]，6. インターフェロン，リバビリンなどの抗ウイルス剤の免疫系を介しての HIV ウイルス動態，HAART 薬剤との相互作用[14] である。

今回，移植先進国である米国で HIV 陽性患者に対する肝移植を積極的に施行しているマイアミ大学のデータを解析した。本邦でも，特に血液製剤による HIV-HCV 重複感染患者で，すでに肝硬変となっている患者約 50 例，また慢性肝炎患者の約 400 例が今後本邦でも肝移植適応となってくる可能性があり，十分な情報集約が必要となる[5]。前出の小池班ガイドラインでは，HIV-HCV 重複感染例に対する肝移植として，東京大学 6 例，広島大学 1 例を報告している[10]。また，血友病保因者よりの生体肝移植も 2002 年に報告されており[15]，実際は 10 例ほどの生体肝移植が施行されているようである。情報の集約化が本患者群に対する肝移植成績の向上には不可欠であり，今後の報告が待たれる。

免疫抑制剤については通常のタクロリムスの投与期間，投与量を調節することで，HAART の併用を行うことが可能であった。実際の個々の患者の免疫抑制剤の投与量，トラフ値と HAART 薬剤の投与タイミングをグラフ化した。各症例でトラフ値は様々であったが，前半は過剰投与によるタクロリムストラフ値の overshoot 傾向がみられた。後半は，おそらく経験値の上昇により，1 週間に 1 回投与などの工夫により通常の免疫抑制レベルで落ち着いている症例が多かった。最近は raltegravir などカルシニューリン阻害薬と相互作用を持たないとされる HAART も可能となっており，肝移植例での仕様につき，今後の報告が待たれる[16]。HAART 再開始時期に関しては，術前に投与していた薬剤を可及的早期に再開するのが望ましいと考えられるが，患者の腎機能，移植肝機能を考慮しつつ，徐々に再開されているのが実情であった。

最近のフランスからの 14 例の報告では，インターフェロン，HAART，肝線維化などの詳細な報告がなされている[7]。全例，術前血中 HIV 量は検出感度以下で，CD4+T 細胞数は 85～1,015 と幅があった。カルシニューリン阻害剤はタクロリムスを 0.5 mg/週で基本的には術後 2 週間目より開始されているが，それでも 5 例 (36%) で過剰投与と

なっていた。またHAARTも術後2週目より再開されていた。肝移植後12カ月目の肝生検ではFCH 1例，F3 1例，F2 2例，F1 5例であった。移植予後は1例をFCHにより失ったのみであり，encouragingな成績であると考えられる。

本邦では血友病患者に対して過去に投与された汚染血液が原因となっていることが多いため，術中，術後の移植肝が機能を発揮開始するまでの凝固，出血管理が困難であることがあげられる。マイアミ大学での検討では血友病患者は1例のみしか含まれておらず，本点については参考とならなかった。また，本邦では法改正により脳死下臓器提供が増加しているものの，全肝移植である脳死肝移植は待機期間が長く，部分肝移植である生体肝移植がいまだ中心的な役割を果たしている。よって，部分肝移植であることの欠点，つまりsmall-for-size症候群の出現，初期移植肝機能遅延，移植時の血管グラフトの不足を克服する必要がある[18]。

また，最近，話題となっているHAART実施中の患者での特発性門脈圧亢進症[19]に生じる門脈血栓症患者に対する肝移植成績を考察するため，門脈血栓の有無にて移植成績を比較したが，特に有意差を認めなかった。脳死肝移植では十分な長さの門脈を使用することができ，また血管グラフトの入手も容易であるため今回の結果が得られたのではないかと推測する。生体肝移植の場合は，グラフト血管長が短いため，ジャンプグラフトなども入手が制限されるため，同様の成績が得られるかは，不明である。

以上，マイアミ大学での本研究結果を，本邦での肝移植に外挿し検討することにより，肝移植合併症の頻度を低下させ，成績向上を図ることができると考えられる。

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Ⅰ．外科総論

6．後天性免疫不全症候群（AIDS）*

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村岡いづみ　原　貴信　兼松隆之**

はじめに

ヒト免疫不全ウイルス（human immunodeficiency virus：HIV）感染症は，HIVがリンパ球（主としてCD4陽性リンパ球）に感染し，免疫系が徐々に破壊されていく進行性の疾患である．後天性免疫不全症候群（AIDS）は，HIV感染症の進行により高度の細胞性免疫不全をきたした結果発症する疾患群を総称するものである．本稿では，一般外科医が遭遇するHIV陽性患者に対する外科治療の際の注意点を概説する．また，本邦で最近問題となっているHIVとC型肝炎ウイルス（HCV）重複感染者の現状，特に肝機能障害についても述べる．

Ⅰ．AIDSの歴史・概念

AIDSは，1981年に最初の症例が報告されて以来，その重篤さのため現在でも世界が抱える大きなテーマの一つである．国連合同エイズ計画（UNAIDS）の2010年版報告書によると，2009年でのHIV陽性の成人と小児数は3,330万人と推定されている[1]．本邦でもHIV感染者・AIDS患者数は増加しており，2010年の新規感染者・患者の報告総数は1,503件と7年連続して1,000件を超えている（図1）．このうち感染に気づかずにAIDSを発症した新規患者数は453件で，過去最

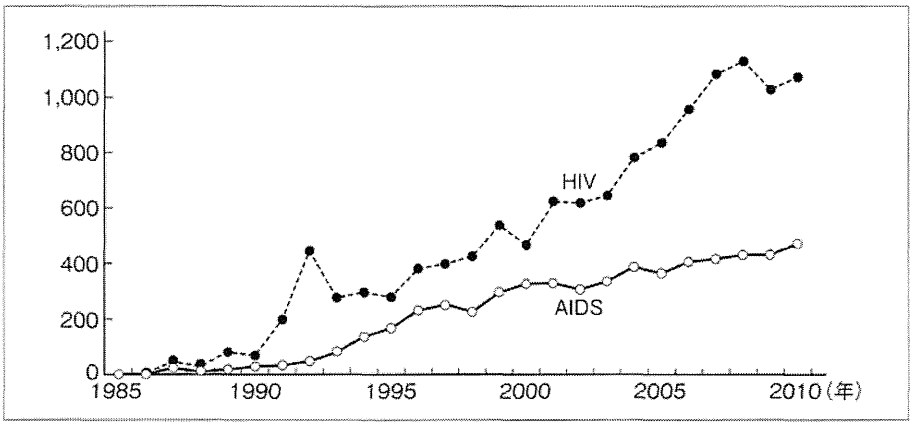

図1．HIV感染者およびAIDS患者報告数の年次推移

キーワード：HIV，AIDS，外科治療，HCV

* Acquired immunodeficiency syndrome（AIDS）
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高と報告されている．感染者の多くは男性であるが，女性の感染者も増加している[2]．

HIV感染症の経過としては，大きく3期に分かれる．急性期を過ぎると，自覚症状のない時期（無症候期）が通常数年続き，さらに進行するとCD4陽性リンパ球抵抗力（免疫）が低下し，下記の日和見感染症などを発症するようになる（図2）．AIDS指標疾患としてはニューモシスチス肺炎，カンジダ症（食道，気道，気管支，肺），クリプトコッカス症（肺以外），活動性結核などの23疾患が規定されている（表1）．現在は適切な時期に抗HIV療法を開始するとAIDS発症を予防することが可能となっている[3]が，診断が遅れるとAIDSが発症する危険性が高まる．AIDS指標疾患以外では，次のような症状がHIV感染症発見の契機となることが多い．性感染症の現病・既往歴，繰り返す帯状疱疹，A型肝炎，B型肝炎，赤痢アメーバ症，脂漏性皮膚炎，口腔内カンジダ症，乾癬，掻痒性丘疹，不明熱・下痢など．医療者は，受診者の疑わしい症状やリスクに注意を払い，積極的に早期発見に努める必要がある．種々の合併症で医療機関を受診したにもかかわらずHIV感染症が見逃され，AIDS発症にいたる例はいまだに多い．

Ⅱ．診断法，治療，予後

HIV感染症の診断には，血清中の抗HIV抗体やHIV（抗原，遺伝子）の検査が行われる．まず粒子凝集反応（PA法），ELISA法などの高感度スクリーニング検査を行うが，0.3％ほどの偽陽性があるため，陽性の場合はHIV-RNA PCR法，Westernブロッティング法で確定診断を得る．HIVに感染してから血液中にHIV抗体が検出されるまで通常6～8週を要するが[4]，近年用いられるHIVスクリーニング検査（第4世代）は抗体検査に抗原検査（HIV-1 p24抗原）を組み合わせたものであり，感染から検査が陽性になるまでのウインドウピリオドは最短2週間程度まで短縮し

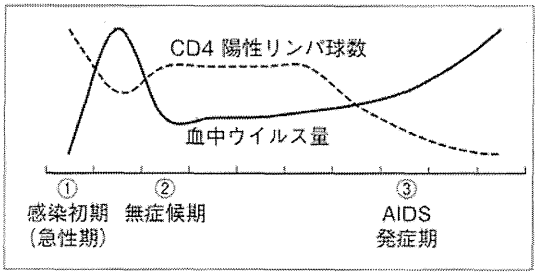

図2．HIV感染症の自然経過

表1．AIDS指標疾患

・カンジダ症（食道，気道，気管支，肺）	・反復性肺炎
・クリプトコッカス症（肺以外）	・サイトメガロウイルス感染症（生後1ヵ月以後で，肝・脾・リンパ節以外）
・コクシジオイデス症	・単純ヘルペスウイルス感染症（①1ヵ月以上継続する粘膜，皮膚の潰瘍を呈するもの，②生後1ヵ月以後で気管支炎，肺炎，食道炎を併発するもの）
・ヒストプラズマ症	・進行性多巣性白質脳症
・ニューモシスチス肺炎	・Kaposi肉腫
・トキソプラズマ脳症（生後1ヵ月以後）	・原発性脳リンパ腫
・クリプトスポリジウム症（1ヵ月以上続く下痢を伴ったもの）	・非Hodgkinリンパ腫
・イソスポラ症（1ヵ月以上続く下痢を伴ったもの）	・浸潤性子宮頸癌
・化膿性細菌感染症（13歳未満）	・リンパ性間質性肺炎・肺リンパ過形成（13歳未満）
・サルモネラ菌血症（再発を繰り返すものでチフス菌によるものを除く）	・HIV脳症
・活動性結核（肺結核または肺外結核）	・HIV消耗性症候群
・非結核性抗酸菌症（①全身に播種したもの，②肺，皮膚，頸部，肺門リンパ節以外の部位に起こったもの）	

ている．感染から数週間以内にインフルエンザに似た症状が出ることがあるが，症状からはそれがHIV感染によるものか否かを判断することはできず，上記検査ではじめて感染が確認される．早期発見・早期治療が発症防止や感染拡大阻止にも結びつくものであることから，無料・匿名で受けられる保健所などでのHIV検査を積極的に利用することが望まれる．

1990年代後半以降，強力な多剤併用療法（highly active anti-retroviral therapy：HAART）によりHIVのコントロールは大幅に改善した．HAARTでは血中ウイルス量を検出感度以下に抑え続けることを目標に，①核酸系逆転写酵素阻害薬（NRTIs），②非核酸系逆転写酵素阻害薬（NNRTIs），③プロテアーゼ阻害薬（PI）を通常①+② or ③の組み合わせで投与する．それによりHIV感染症の進行を抑え免疫能を保持し，QOLやHIV感染に関連した臨床症状を改善し，死亡を減らすことをめざす．この目標を達成するには，抗HIV療法に対する服薬アドヒアランスが重要である．服薬率が95％以下の場合，半数以上が治療不成功といわれている[6]．最近はCD4陽性リンパ球数500/μl未満となった場合の治療開始が推奨されているが，妊婦や心・腎・肝疾患を有する患者では，CD4陽性リンパ球数の値にかかわらず治療開始が推奨される[7]．治療中断は予後を悪化させることが大規模無作為試験で明らかとなっており，治療をいったん開始したら重篤な副作用や服薬不能な状態など特別な場合を除き，治療を中断してはならない[8]．周術期も可及的継続が望まれるが，中途半端な内服や中断と再開の繰り返しは耐性ウイルス出現の危険性を高めるため，専門家への相談が望ましい．

Ⅲ．HIV感染患者での外科的治療とその注意点

HIV陽性患者の外科手術として多いものはリンパ節生検，虫垂炎，肛瘻炎，肝膿瘍，腸管感染症，痔瘻などで，原虫，一般細菌，一般ウイルスによる感染症があげられる[9-11]．近年，HIV陽性患者であってもHAARTにより非感染者と同様な生命予後を期待できるため，長期生存に伴い主要な死因として動脈硬化性疾患，AIDS指標疾患に含まれない悪性疾患，加齢に伴う疾患が増加している．この傾向は今後もかわらず，外科治療の必要性が増加するものと考えられる．

通常のHIV陽性患者に対する外科治療適応は，①全身状態が落ち着いている（AIDS未発症），②CD4陽性リンパ球数が200/μl以上，③インフォームド・コンセントが得られることとされている[10,11]．外科治療を行うためには免疫状態の把握が必要であり，臨床症状のほか，術前のCD4陽性リンパ球数，HIV-RNA量が重要である．特にCD4陽性リンパ球数は抗ウイルス療法開始の目安と日和見感染のリスクを示している．

HIV患者の手術リスクは，non-HIVと比較してそれほど大きくはないものの，術後肺炎のリスクは高く，HIV量が30,000 copy/ml以下が望ましいという文献もある[12]．しかし，HAARTの出現とともにHIVのコントロールが良好となり，HIV感染症はもはや外科手術の独立した危険因子とはなりえず，患者の全身状態と疾患そのもののリスクによって手術適応を決めるべきであるといわれている[13,14]．なお，手術を受けたために周囲にHIV感染を知られることがないよう，患者家族への説明の際は配慮が必要であり，誰がどこまで病気のことを知っているのかは必ず把握すべきである．

❶ 医療従事者の感染リスク

医療従事者におけるHIV感染血液による針刺し・切創などの職業曝露からHIVの感染が成立するリスクは，経皮的曝露では約0.3％[1]，粘膜曝露では約0.09％[2]と報告されている[15]．この感染危険率は，B型肝炎ウイルス（曝露源がHBe抗原陽性の場合で約40％，抗HBe抗体陽性の場合で約10％）やHCV（約2％）に比べると明らかに低いと考えてよい．米国では，2001年6月までに57名の医療従事者が職業上の曝露によりHIVに感染しており，その他にもさらに137件の事例についてもHIV職業感染の可能性が考えられているが，曝露後予防として抗HIV薬3剤併用が行われるようになってから，職業曝露によるHIV感染はほとんど報告されていない．本邦では2011年1月の時点でHIV職業感染の報告例はないが，HIV感染患者数は増加を続けており，事前に対策を立てておくことがきわめて重要である．

表2. 感染予防策

A. 標準予防策
　日常業務（手洗いはすべての業務に必須）
　　手洗いの徹底（入室時，ケア時，退室時のアルコール性手指消毒剤の使用）
　手術など侵襲的な手技
　　①通常の手術と同様，②マスクはフェイスシールド付きマスクあるいはサージカルマスクとゴーグルの併用，③足は鋭利物の落下による針刺しを防ぐ目的で，全面をおおう靴あるいは同様の機能をもつものが必要，④足カバーは必ずしも必要ではない
　気道内吸引など，体液の飛散を発生させる手技
　　①手袋，フェイスシールド付きマスクあるいはサージカルマスクとゴーグルの併用，長袖ガウンあるいは長袖エプロン，②ディスポーザブル吸引瓶の使用
　血液・体液の飛散リスクのある手技
　　①手袋，②飛散が想定される場合には，長袖ガウンあるいは長袖エプロン・フェイスシールド付きサージカルマスク
B. 血液媒介感染対策
　針刺し，粘膜曝露を防御する対策
　　①鋭利物の使用にあたり，ディスポーザブルの製品は必ず処置者が廃棄まで完了して，次の処置・手技へと移行する
　　②バイオハザードボックスは使用する器具の形状・大きさに合った携帯型シャープスコンテナーを処置実施場所まで携帯する．大きさに合う携帯型シャープスコンテナーがない場合には，据え付き型ハザードボックスの使用を考慮してもよい
　　③粘膜曝露予防対策の基本は，血液・体液の飛散リスクのある処置時に，必要な防護具を着用すること
　　④リキャップなど感染リスクのある方法は絶対禁忌

❷ 医療従事者における感染予防策と曝露時対策[16]

a. 感染予防策

HIV感染者に対する外科治療における感染経路は主として血液媒介によるものであり，一部には飛散などによる粘膜や損傷皮膚を介することも想定される．現実的には，曝露が生じてしまった場合の対策（後述）を除き，HIVに対する特殊な感染対策を講じる必要はなく，通常の感染予防策（標準予防策）が基本とされる（表2）．標準予防策とは，直接接触による感染予防策を中心とするものであり，対象はすべての患者の汗以外の体液である．実施する手技・手術によっては体液の飛散を考慮した対策が必要となる．

鋭利器材（針など）については，極力ディスポーザブルのものを使用することで再使用を避け，使用後の手術器具の受け渡しの際にセーフティゾーンを介することで鋭利器材の直接手渡しを避ける配慮を行っている施設もある．

b. 体液曝露後の対策

体液曝露後の対策は図3のフローチャートのような各院のシステムに従ってすみやかに実施する．フローチャートにある適切な予防処置とは，曝露部位の流水による洗浄，責任者への報告なども含む．

Ⅳ. HIV-HCV重複感者の治療

米国のHIV感染患者の25～30％はHCVを重複感染しているとされ，合計では約30万人がHIV-HCV重複感染と推計されている[17]．本邦では，血友病など血液疾患に対する過去の汚染血液製剤使用によるHIV-HCV重複感染者がほとんどである．最近ではHAARTの発達によりHIV感染症自体による死亡が減少した結果，約半数が肝関連疾患で死亡するといわれている[18]．

非HIV感染患者と比し肝硬変への進行が早く，肝不全の状態となり，長期予後が望めない患者は肝移植の適応となることがある[19]．また，肝不全にはいたっていないが肝障害が高度となり，HAARTの継続が困難な場合や経過中に肝細胞癌を発症した場合も適応とされる．HAART施行中の患者では肝予備能，HIV感染症の状況の双方か

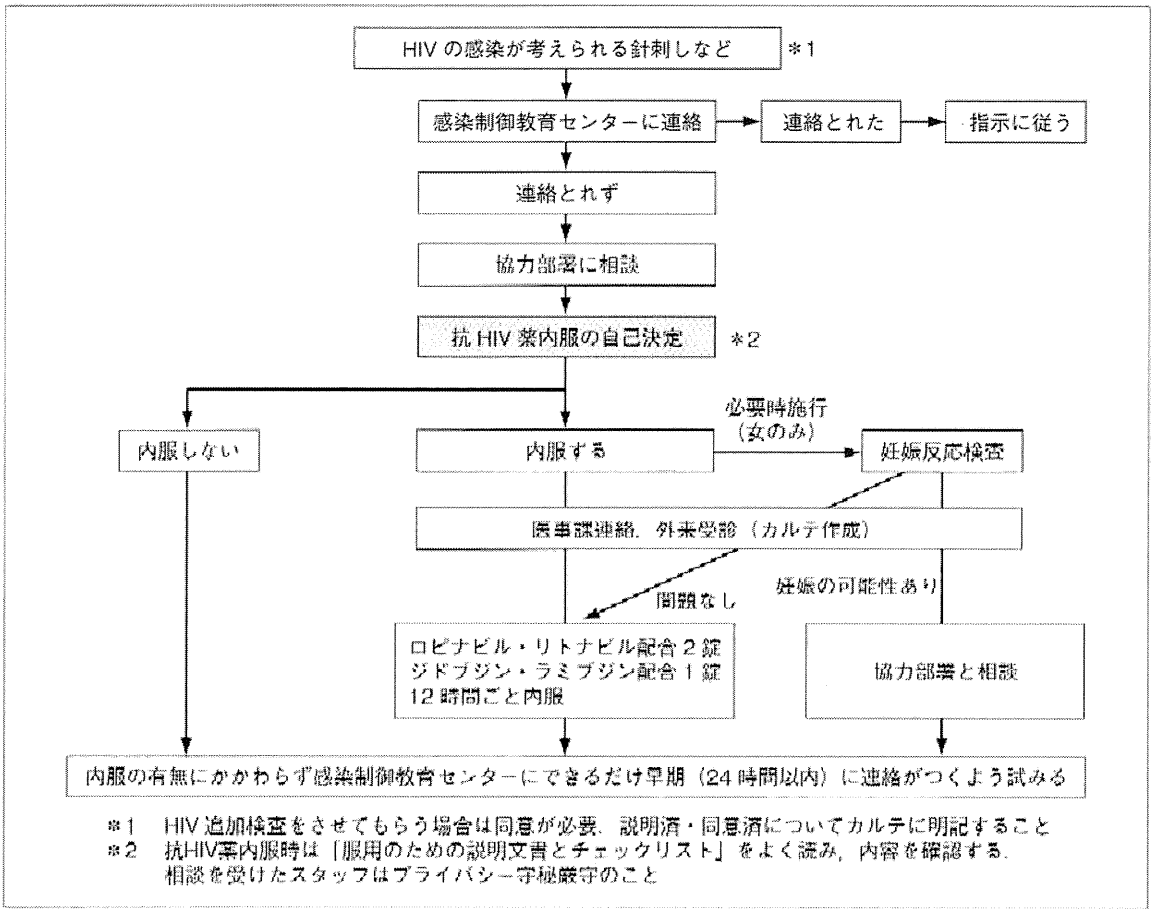

図3．HIV感染予防フローチャート（長崎大学）

らの適応検討が必要である．

肝移植のための条件としては，①AIDSを発症していないこと，②CD4陽性リンパ球数が200～250/μl以上であること，③HAARTによって血中HIV量が測定感度以下であることがあげられることが多い．しかし，門脈圧亢進症による汎血球減少を考慮し，CD4陽性リンパ球数は100/μlより適応と考えている施設もあり，CD4陽性リンパ球数のみで適応を決めてよいのか，今後の検討課題の一つである[10]．

おわりに

HIV感染者の増加により，今後，一般外科医もHIV感染患者の外科治療機会が増加していくものと推測される．免疫不全と外科手術のリスク，免疫不全に伴う独特な鑑別疾患，周術期の抗HIV薬中断法，薬物相互作用などさまざまな注意点が存在する．しかし，HIVの専門家への相談を早期に行うことで患者治療を円滑にすすめ，また医療関係者への二次感染を避けることができると考えられる．

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The incidence of hepatocellular carcinoma associated with hepatitis C infection decreased in Kyushu area

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Summary

Background: The incidence of hepatocellular carcinoma (HCC) in Japan has still been increasing. The aim of the present study was to analyze the epidemiological trend of HCC in the western area of Japan, Kyushu.

Material/Methods: A total of 10,010 patients with HCC diagnosed between 1996 and 2008 in the Liver Cancer study group of Kyushu (LCSK), were recruited for this study. Cohorts of patients with HCC were categorized into five year intervals. The etiology of HCC was categorized to four groups as follows; B: HBsAg positive, HCV-RNA negative, C: HCV-RNA positive, HBsAg negative, B+C: both of HBsAg and HCV-RNA positive, non-BC: both of HBsAg and HCV-RNA negative.

Results: B was 14.8% (1,485 of 10,010), whereas 68.1% (6,819 of 10,010) had C, and 1.4% (140 of 10,010) had HCC associated with both viruses. The remaining 1,566 patients (15.6%) did not associate with both viruses. Cohorts of patients with HCC were divided into six-year intervals (1996–2001 and 2002–2007). The ratio of C cases decreased from 73.1% in 1996–2001 to 64.9% in 2002-2007. On the other hand, B and -nonBC cases increased significantly from 13.9% and 11.3% in 1996-2001 to 16.2% and 17.6% in 2002-2007, respectively.

Conclusions: The incidence of hepatocellular carcinoma associated with hepatitis C infection decreased after 2001 in Kyushu area. This change was due to the increase in the number and proportion of the HCC not only nonBC patients but also B patients.

key words: hepatitis virus • hepatocellular carcinoma • Japan

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BACKGROUND

The three leading causes of death in Japan are malignancy neoplasms, cardiovascular diseases, and cerebrovascular diseases. Since 1981, malignant neoplasms have been the leading cause of death in Japan. For the last 30 years, liver cancer has been the third leading cause of death from malignant neoplasms in men. In women, liver cancer has ranked fifth during the past decade [1]. Hepatocellular carcinoma (HCC) accounts for 85% to 90% of primary liver cancers[2] and the age-adjusted HCC mortality rate has increased in recent decades in Japan [3]. Similarly, a trend of increasing rates of HCC has been reported from several developed countries in North America, Europe and Asia [4,5]. HCC often develops in patients with liver cirrhosis caused by hepatitis B virus (HBV), hepatitis C virus (HCV), excessive alcohol consumption, or nonalcoholic fatty liver disease. Of the hepatitis viruses which cause HCC, HCV is predominant in Japan [6–9].

Although the age-adjusted incidence of HCC has increased in Japan, sequential changes in etiology of HCC patients between 2001 and 2008 are not fully understood [10]. To clarify factors affecting epidemiological changes in Japanese HCC patients, especially the recent trend of HCC, we analyzed the epidemiological trend of HCC in the western area of Japan, Kyushu area.

MATERIAL AND METHODS

Patients

A total of 10,010 patients with HCC diagnosed between 1996 and 2008 in the Liver Cancer study group of Kyushu (LCSK), were recruited for this study. The diagnosis of HCC was based on AFP levels and imaging techniques including ultrasonography (USG), computerized tomography (CT), magnetic resonance imaging (MRI), hepatic angiography (HAG), and/or tumor biopsy. The diagnostic criteria for HCC were either a confirmative tumor biopsy or elevated AFP (≥20 ng/mL) and neovascularization in HAG and/or CT.

Etiology of HCC

A diagnosis of chronic HCV infection was based on the presence of HCV-RNA detected by polymerase chain reaction (PCR), whereas diagnosis of chronic HBV infection was based on the presence of hepatitis B surface antigen (HBsAg). The etiology of HCC was categorized to four groups as follows; **B:** HBsAg positive, HCV-RNA negative, **C:** HCV-RNA positive, HBsAg negative, **B+C**: both of HBsAg and HCV-RNA positive, **nonBC:** both of HBsAg and HCV-RNA negative.

Statistical analysis

The data were analyzed by the Mann-Whitney test for the continuous ordinal data, the x2 test with Yates' correction and the Fisher exact test for the association between two qualitative variables. The standard deviation was calculated based on the binomial model for the response proportion. $P<0.05$ was considered statistically significant.

RESULTS

Clinical features of the studied patients

A total of 10,010 patients with HCC were diagnosed at our study group from 1996 to 2008. Table 1 show that the proportion of patients diagnosed with **B** was 14.8% (1,485 of 10,010), whereas 68.1% (6,819 of 10,010) had **C**, and an additional 1.4% (140 of 10,010) had HCC associated with both viruses. The remaining 1,566 patients (15.6%) did not associate with both viruses. In analysis of patients in HCC by category, the median age of patients at diagnosis of **B** was 57 years old significant younger than other types HCC(**C: 69, nonBC: 70,.B+C 65 years old**).

As shown in Figures 1 and 2, the number and ratio of **B** cases remained unchanged from1996 to 2001 and thereafter increased and plateaued, whereas **C** rapidly increased from 1996 to 2000 and thereafter decreased and plateaued. In addition, the number and ratio of the **nonBC** cases has increased continued gradually and continued in this study period.

Change of etiology in patients with HCC during the period 1996–2007 with 6-years intervals

Cohorts of patients with HCC were divided into six-year intervals (1996–2001 and 2002–2007). Table 2 show that the incident rate of **C** decreased significantly from 73.1% in 1996-2001 to 64.9% in 2002-2007 (1996–2001 vs. 2002–2007, $p=<0.001$). On the other hand, the incident rate of **B** and **-nonBC** increased significantly from 13.9% and 11.3% in 1996-2001 to 16.2% and 17.6% in 2002-2007, respectively. Not only the incident rate but also number of **B** and **-nonBC** became larger in same 6 years periods.

Table 3 shows that male/female ratio of **C** and **-nonBC** decreased significantly from 2.2 and 4.0 in 1996-2001 to 1.8 and 2.7 in 2002-2007, respectively ($p\leq0.001$). The ratio became clearly smaller, indicates an increase in female patients with **C** and **nonBC.** On the other hand, the male/female ratio of **B** patients did not significantly change during the period. The median age at diagnosis of **B, C**, and **nonBC** in six-year intervals were significant increase from 56 to 58, from 67 to 71 and from 68 to 71 years of age during the period.

DISCUSSION

Our study was the twenty-three major liver center-based study designed to examine the sequential change in the background of HCC patients during the past 13 years, 1996–2008. More than 80% of our patients had chronic HBV or HCV infections. During this observation period, the number and proportion of HCC-C reached a peak in 2000 and thereafter decreased and became stabilized. Previous studies from Japan reported that the proportion of the HCC patients with HCV infection had been increased and reached a plateau in the period of 1981–2001 [1,3,10–12]. However, in our study, the number and proportion of the HCC patients with HCV infection cases decreased in 2001–2008. The reason may be explained as follows; interferon therapy for chronic hepatitis C may have been associated with a decreased incidence of HCC [13–17]. Oral supplementation with a oral branched-chain amino acids has been useful in the prevention HCC [18]. Finally, the chronically HCV-infected

Table 1. The characteristic of HCC patients during the period of 1996–2008.

Age (y.o.)	B		C		nonB		B+C		Total
	Male	Female	Male	Female	Male	Female	Male	Female	
0–	1	0	0	1	0	0	0	0	**2**
10–	4	1	0	0	0	2	0	0	**7**
20–	6	2	1	0	1	1	0	0	**11**
30–	31	5	4	0	11	3	2	0	**56**
40–	204	22	130	12	32	15	12	0	**427**
50–	507	66	728	145	167	32	31	6	**1,682**
60–	287	118	1836	741	411	102	35	13	**3,543**
70–	140	64	1775	947	483	133	22	14	**3,578**
80–	9	18	271	214	97	65	1	4	**679**
90–	0	0	9	5	9	2	0	0	**58**
Total	**1,189**	**296**	**4,754**	**2,065**	**1,211**	**355**	**103**	**37**	**10,010**
	1,485 (4.8%)		6,819 (68.1%)		1,566 (15.6%)		140 (1.4%)		
Median	57	63	67	70	68	70	61	68	**67**
	57		69		70		65		
Mean	56	64	68	71	69	71	62	68	**67**
	58		68		68		63		
Range	1–87	14–89	27–94	0–93	28–96	17–90	36–82	55–82	**0–96**
	1–89		0–94		17–96		36–82		

Age: B vs. C p≤0.001; B vs. B+C p≤0.001; B vs. nonBC p≤0.001; C vs. BC p≤0.001; C vs. nonBC p=0.043; BC vs. nonB+C p≤0.001. IQR – interquartile range; SD – standard deviation.

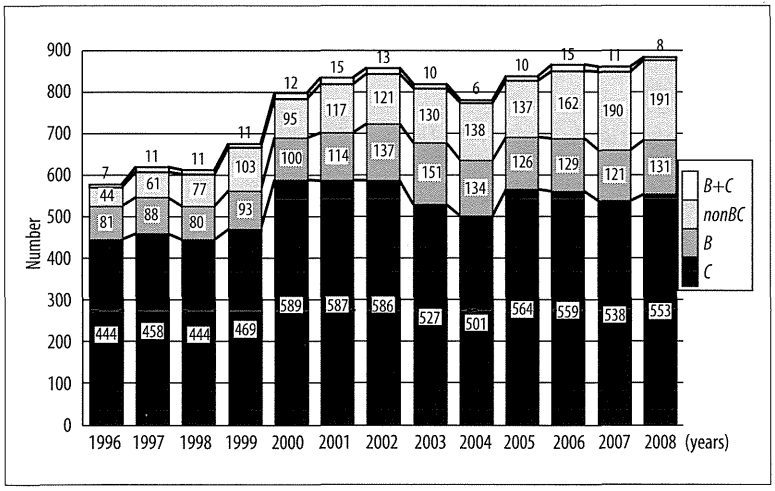

Figure 1. Sequential changes in the number of HCC patients categorized by etiology during the period 1996–2008.

population is aging in Japan. Yoshizawa et al. reported that age-specific prevalence for the presence of HCVAb among ~300,000 voluntary blood donors from Hiroshima in 1999 clearly increased with the age, reaching the highest proportion of 7% in individuals who were more than 70 years old [10,19]. In this study, the median age of the HCC patients with HCV infection steadily increased from 67 to 71 years of age during the studied period. In a word, HCV infected people become older with years in Japan and they were regarded as a high risk for HCC.

The prevalence rate of HBV in Kyushu area has been reported to be higher than other area in Japan [1]. In Kyushu area, 95% of patients with chronic HBV infection had HBV genotype C except for Okinawa [20]. HBV genotype C is thought to be associated with higher incidence of HCC

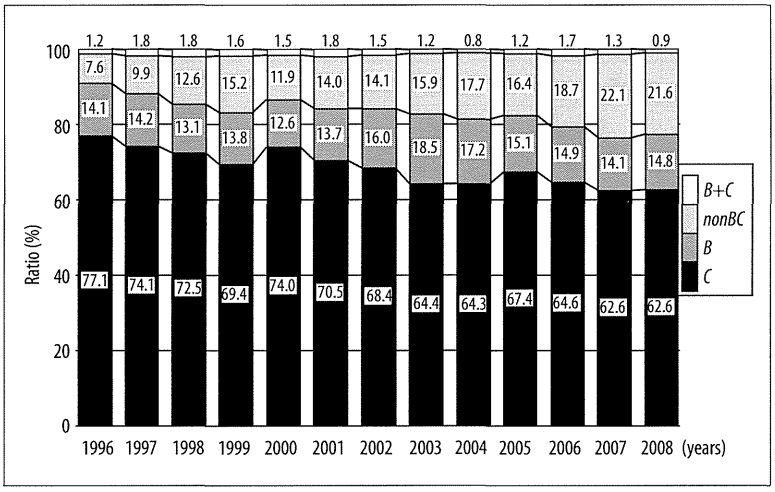

Figure 2. Sequential changes in the ratio of HCC patients categorized by etiology during the period 1996–2008.

Table 2. Change of etiology in patients with HCC during the period 1996–2007 with 6-years intervals.

Period		1996–2001	2002–2007	P value
Number		3,023	4,173	
Sex	Male	2,162	2,849	
	Female	861	1,324	
Ratio (male/female)		2.5	2.2	0.003
Age (y.o.) (IQR)		66 (14)	69 (12)	<0.001
Hepatitis virus (%)	B	13.9	16.2	
	C	73.1	64.9	
	B+C	1.7	1.3	
	nonBC	11.3	17.6	0.001

QR – interquartile range.

Table 3. The median age and male/female ratio of HCC patients during the period of 1996–2007.

Period		1996–2001	2002–2007	P value
B				
Age (y.o.) (IQR)		56 (14)	58 (15)	0.001
Sex	Male	331	519	
	Female	88	157	
Ratio (male/female)		3.8	3.3	0.391
C				
Age (y.o.) (IQR)		67 (9)	71 (11)	<0.001
Sex	Male	1,524	1,753	
	Female	687	955	
Ratio (male/female)		2.2	1.8	0.002
nonBC				
Age (y.o.) (IQR)		68 (12)	71 (13)	<0.001
Sex	Male	273	534	
	Female	69	201	
Ratio (male/female)		4.0	2.7	0.012

QR – interquartile range.

compared with other HBV genotypes [21]. In the present study, the incident rate of HCC patients with HBV infection became larger in this study period. To explain this change, we must consider from two viewpoints. The one is that the number of patients with HCC caused by HCV infection decreased, the other is that the proportion of chronic HBV infected patients who have reached the age of developing HCC is relatively high as described below.

Nationwide health survey for HBsAg in the over 40 years of age population had been done between 2002 and 2006 in Japan. This survey reports indicated that the average HBsAg prevalence was 1.2% in the total Japanese population patients with chronic HBV infection [10] and the age-specific prevalence of HBsAg was higher in the group aged between 50 (1.4%) and 55 years (1.5%). In the HCC patients with HBV genotype C, the mean age was 55 years in Japan [20]. This overlap between age-specific prevalence and hepatocellular carcinogenic age would be associated with the increase of HCC patients with HBV infection. Nucleoside analogue reverse transcriptase inhibitor (NARTI) therapy effectively reduces the incidence of HCC in chronic hepatitis B patients [22,23]. However, Interferon therapy for chronic hepatitis C started from 1992, whereas NARTI therapy for HBV started from 2000 in Japan [24,25]. Hence, HBV associated HCC will probably decrease in Japan during the next 10 to 20 years.

The survey of HCC patients associated with nonBC infection in Japan was conducted by Inuyama Hepatitis Research Group from 1995 to 2003. The ratio of HCC patients with nonBC accounted 9.3% [1]. In the present study, the ratio of HCC patients with nonBC was 14.1%. Furthermore, the number and the proportion of HCC patients with nonBC have been gradually increasing in the periods. The current two studies account for the increase in number and proportion of HCC patients with nonBC. First, Lai et al. reported

that type 2 diabetes increases the risk of developing HCC in those who are HCV negative or have a high level of total cholesterol [26]. Second, Nakano et al. reported that epidemiological studies on diabetes mellitus revealed that the number of patients with diabetes mellitus is gradually increasing in Japan along with development of car society and westernization of food intake. Since prevalence of diabetes mellitus increases with aging, proportion of individuals with diabetes mellitus aged over 60 has exceeded two-third of estimated total number of patients (7.40 million in 2002) in Japan where aging of society is rapidly progressing [27]. In a word, the number of type 2 diabetes people is increasing in Japan and they were regarded as a high risk for HCC. Then, the number and the proportion of HCC patients with nonBC have been increased recent twelve years in Japan.

It is known that 2 to 4 decades of chronic HCV infection are required to develop cirrhosis and subsequent HCC [28–31]. The number of HCC cases has increased in Japan, because individuals infected with HCV during the past have grown old and have reached the cancer-bearing age. The prevalence of HCV infection in young Japanese individuals is low and the incidence of HCVAb is very low because of preventative actions against HCV infection such as the screening of blood products for HCV and the use of sterile medical equipment [32]. Additionally, we showed that the number and proportion of patients with HCC-C cases decreased, whereas the number and ratio of HCC-nonBC steadily increased during the studied period. These findings may be expected that the incidence of HCC patients with nonBC in Japan may continue to increase even after the consequence of the HCV epidemic level off, a country that is far advanced with regard to HCC patients with HCV infection, in the near future.

Conclusions

In summary, HCC patients had increased from 1996 to 2000 and this increase was originated from HCC patients with HCV infection. The number and proportion of HCC patients with HCV infection reached a peak in 2000 and thereafter decreased and became stabilized. The incidence of hepatocellular carcinoma associated with hepatitis C infection decreased after 2001 in Kyushu area. This change was due to the increase in the number and proportion of the HCC not only nonBC patients but also B patients.

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Original Article

Data mining reveals complex interactions of risk factors and clinical feature profiling associated with the staging of non-hepatitis B virus/non-hepatitis C virus-related hepatocellular carcinoma

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Aim: Non-hepatitis B virus/non-hepatitis C virus-related hepatocellular carcinoma (NBNC-HCC) is often detected at an advanced stage, and the pathology associated with the staging of NBNC-HCC remains unclear. Data mining is a set of statistical techniques which uncovers interactions and meaningful patterns of factors from a large data collection. The aims of this study were to reveal complex interactions of the risk factors and clinical feature profiling associated with the staging of NBNC-HCC using data mining techniques.

Methods: A database was created from 663 patients with NBNC-HCC at 20 institutions. The Milan criteria were used as staging of HCC. Complex associations of variables and clinical feature profiling with the Milan criteria were analyzed by graphical modeling and decision tree algorithm methods, respectively.

Results: Graphical modeling identified six factors independently associated with the Milan criteria: diagnostic year of HCC; diagnosis of liver cirrhosis; serum aspartate aminotransferase (AST); alanine aminotransferase (ALT); α-fetoprotein (AFP); and des-γ-carboxy prothrombin (DCP) levels. The decision trees were created with five variables to classify six groups of patients. Sixty-nine percent of the patients were

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within the Milan criteria, when patients showed an AFP level of 200 ng/mL or less, diagnosis of liver cirrhosis and an AST level of less than 93 IU/mL. On the other hand, 18% of the patients were within the Milan criteria, when patients showed an AFP level of more than 200 ng/mL and ALT level of 20 IU/mL or more.

Conclusion: Data mining disclosed complex interactions of the risk factors and clinical feature profiling associated with the staging of NBNC-HCC.

Key words: data mining, disease progression, hepatoma, non-viral hepatitis, tumor marker

INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) is the fifth most common cancer and the third most common cause of cancer-related deaths worldwide.[1–3] Chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) is a risk factor for HCC. Recent developments in the management of patients with viral hepatitis have resulted in early detection of HCC and improvement of prognosis.[4–8]

The number of patients with non-HBV/non-HCV-related HCC (NBNC-HCC) has been increasing, and NBNC-HCC now accounts for 12–16% of all the HCC cases in Japan.[8,9] A variety of factors are involved in the development and progression of this cancer including age, sex, alcoholic liver disease and diabetes mellitus.[10–12] Therefore, neither early detection nor improved prognosis has been achieved in NBNC-HCC.[6] Radical treatment is applicable to patients with NBNC-HCC who meet the Milan criteria;[13] however, this cancer is often detected at an advanced stage. For earlier detection, it is important to understand the complex interactions of the risk factors and clinical feature profiling associated with the Milan criteria, a staging system for NBNC-HCC.

Data mining, a set of statistical techniques, uncovers meaningful patterns and interactions of variables from a large data collection even when there is no a priori hypothesis imposed.[13] Graphical modeling is an exploratory multivariate analysis of data mining that reveals complex associations between variables.[14] This analysis assumes that the response variable is influenced by multiple factors.[15] Therefore, different from results of univariate analysis, an association between a risk factor and an outcome variable may disappear or appear because of the effects of another set of variables known as "confounding factors".[16,17] Furthermore, its findings are visualized as a graph, which provides an idea of how variables interact and denotes the conditional independence structure between random variables.[15] Therefore, graphical modeling is now identified as a new approach to model clinical data.[18]

Decision tree making is another exploratory technique of data mining that represents a series of rules for classification by identifying priorities.[19–21] It is an explicit, quantitative and systematic approach to decision-making under conditions of uncertainty and allows clinicians to choose an option that maximizes the net benefit to the patient.[22] Recently, decision trees were used to reveal the clinical feature profiling for staging of pancreatic cancer[23] and ovarian cancer.[24] However, decision trees have never been applied to identify the clinical feature profiling associated with the staging of NBNC-HCC.

The aims of this study were to reveal complex interactions of the risk factors and clinical feature profiling associated with the staging of NBNC-HCC using data mining techniques.

METHODS

Patient database

BETWEEN 1995 AND 2006, a total of 10 133 patients were diagnosed with HCC at 23 institutions located in Kyushu, a high morbidity area of HCC in Japan. Among them, 1363 patients were diagnosed with NBNC-HCC according to the negative results of both serum hepatitis B surface antigen and serum anti-HCV antibody or HCV RNA.

In order to examine the clinical variables associated with the staging of NBNC-HCC, a database of 663 patients with NBNC-HCC at 20 institutions was created on the basis of the following variables: diagnostic year of HCC; age; sex; family history of liver disease; past history of blood transfusion; alcohol intake; diagnosis of liver cirrhosis; diagnosis of liver disease; diagnosis of diabetes mellitus; serum aspartate aminotransferase (AST) level; serum alanine aminotransferase (ALT) level; serum α-fetoprotein (AFP) level; serum des-γ-carboxy prothrombin (DCP) level; size of HCC; and number of HCC.

For practical use, alcohol intake, serum AFP level and serum DCP level were categorized as follows. Alcohol intake: none; 60 g/day or less; 60–100 g/day; or more than 100 g/day. AFP level: 20 ng/mL or less; 20–200 ng/mL; or more than 200 ng/mL. DCP level: 40 mAU/mL or less; 40–100 mAU/mL; or more than 100 mAU/mL.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected by the approval of the Ethics Committee of the Kurume University School of Medicine.

Diagnosis and staging of HCC

The diagnosis of HCC was based on the clinical practice manual proposed by the Japan Society of Hepatology,[25] by using serum AFP and DCP levels and imaging techniques including ultrasonography, computerized tomography, magnetic resonance imaging, hepatic angiography and/or tumor biopsy. The Milan criteria (single nodule ≤5 cm or three nodules <3 cm) were used for the staging of HCC.[26]

Data mining

An association between the Milan criteria and each risk factor was examined by Student's *t*-test and χ^2-test. Because of the insufficient scientific evidence for testing specific clinical hypotheses, graphical modeling and decision trees were employed to explore complex associations between the Milan criteria and a set of risk factors.

MIM software (http://www.hypergraph.dk/) was used for graphical modeling. R package rpart (recursive partitioning and regression trees by Terry Therneau and Beth Atkinson; http://www.mayo.edu/biostatistics) was used to construct a decision tree algorithm. In order to evaluate the prediction error, the original data ($n = 663$) were randomly divided into a training dataset ($n = 442$) and a test dataset ($n = 221$). Ten-hold cross-validation was conducted to construct the initial tree on the basis of the training dataset; then, the optimal-size tree was constructed by examining a set of cost–complexity parameters. The overall prediction error rate as well as the sensitivity and specificity were calculated by applying the results of the decision tree algorithm to the test dataset.

RESULTS

Characteristics of patients with NBNC-HCC

THE PATIENTS' CHARACTERISTICS are summarized in Table 1. Family history of liver disease and history of blood transfusion were not noted in more than 80% of the patients. Approximately 40% of the patients did not have any etiology of chronic liver disease.

Univariate analysis of variables associated with the Milan criteria

Univariate analysis showed that diagnosis of liver cirrhosis, serum AST level, serum ALT level, serum AFP level and serum DCP level were significantly associated with the Milan criteria (Table 2).

Table 1 Characteristics of all patients

Variable	
n	663
Diagnostic year of HCC (years)	2002 ± 3
Age (years)	68.1 ± 9.9
Male/female	480/183
Family history of liver disease (yes/no/unclear)	79/547/37
History of blood transfusion (no/before 1989/after 1989/unclear)	584/29/22/28
Daily alcohol intake (none/<60 g/60–100 g/>100 g)	254/183/141/85
Etiology of chronic liver disease (none/alcohol/others)	296/188/179
Diagnosis of liver cirrhosis (yes/no)	260/403
Diagnosis of diabetes mellitus (no/yes without medication/yes with medication)	396/109/158
Serum AST level (U/L)	53.3 ± 51.3
Serum ALT level (U/L)	51.8 ± 49.9
Serum AFP level (ng/mL)	9397 ± 71066
Serum DCP level (mAU/mL)	8003 ± 37377
Size of HCC (cm)	5.0 ± 3.4
Number of HCC	2.8 ± 2.9

Data are expressed as the mean ± standard deviation or the number of patients.
AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DCP, des-γ-carboxy prothrombin; HCC, hepatocellular carcinoma.

Graphical modeling

Complex interactions of the risk factors associated with the Milan criteria were visualized graphically (Fig. 1). Graphical modeling identified six independent factors directly associated with the Milan criteria: diagnostic year of HCC; diagnosis of liver cirrhosis; serum AST level; serum ALT level; serum AFP level; and serum DCP level (Fig. 1). Although alcohol intake, diagnosis of liver disease and diagnosis of diabetes mellitus were not directly associated with the Milan criteria, they were associated with the Milan criteria through diagnosis of liver cirrhosis (Fig. 1).

Decision tree algorithm

With the training dataset ($n = 442$), a decision tree algorithm was created by using five variables to classify six groups of patients (Fig. 2). A serum AFP level of 200 ng/mL or less was the cut-off value for the initial

Table 2 Univariate analysis of the variables associated with the Milan criteria

Variable	Statistical method	Test statistics	Degree of freedom (df)	*P*
Diagnostic year of HCC (years)	χ^2	13.4013	11	0.2679
Age (years)	Pooled	−1.07	661	0.2843
Sex	χ^2	0.2975	1	0.5854
Family history of liver disease	χ^2	1.7412	1	0.187
History of blood transfusion	χ^2	4.9527	2	0.084
Daily alcohol intake	χ^2	2.4158	3	0.4907
Liver cirrhosis	χ^2	28.9521	1	<0.0001
Diabetes mellitus	χ^2	0.926	2	0.6294
AST level (U/L)	Satterthwaite	3.06	387.51	0.0023
ALT level (U/L)	Satterthwaite	4.79	546.95	<0.0001
AFP level (ng/mL)	χ^2	63.1357	2	<0.0001
DCP level (mAU/mL)	χ^2	47.7161	2	<0.0001

Associations between the variables and the Milan criteria were analyzed by the indicated statistical methods. $P < 0.05$ was considered significant.
AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DCP, des-γ-carboxy prothrombin; HCC, hepatocellular carcinoma.

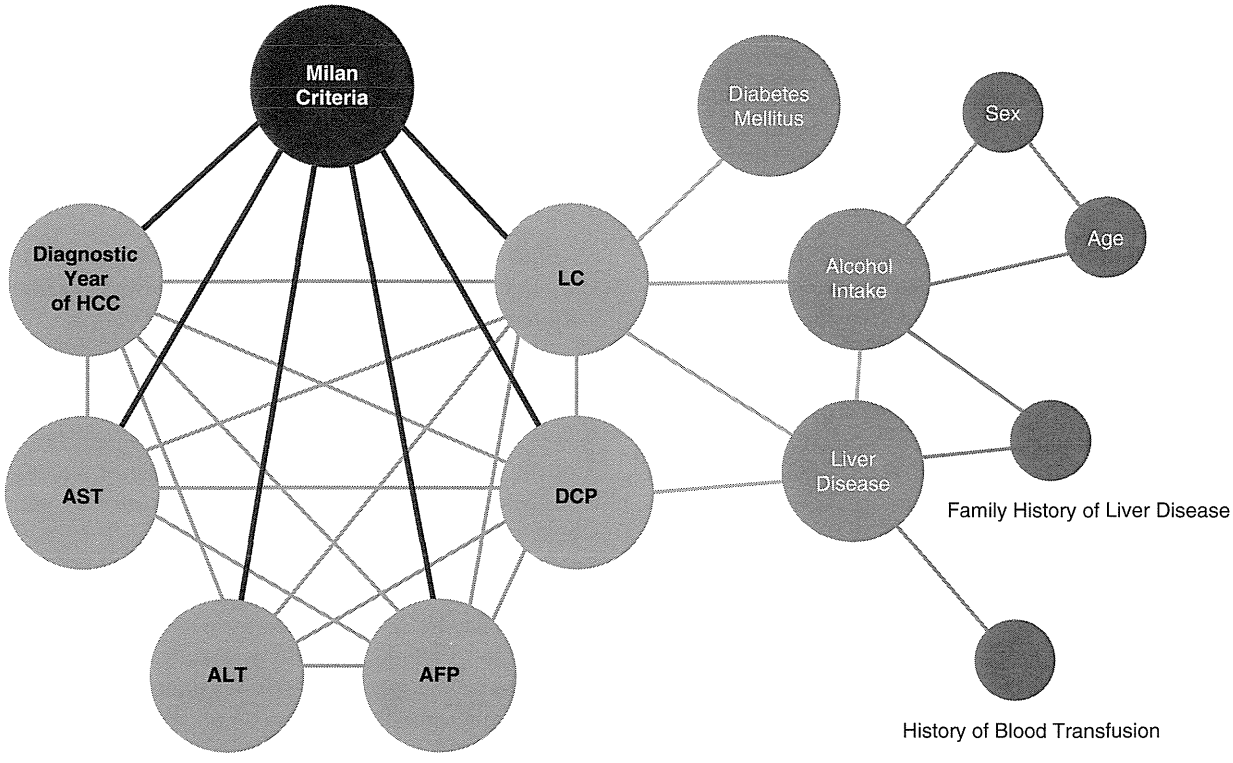

Figure 1 Graphical modeling of the interactions of the risk factors associated with the Milan criteria. AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DCP, des-γ-carboxy prothrombin; HCC, hepatocellular carcinoma; LC, liver cirrhosis.

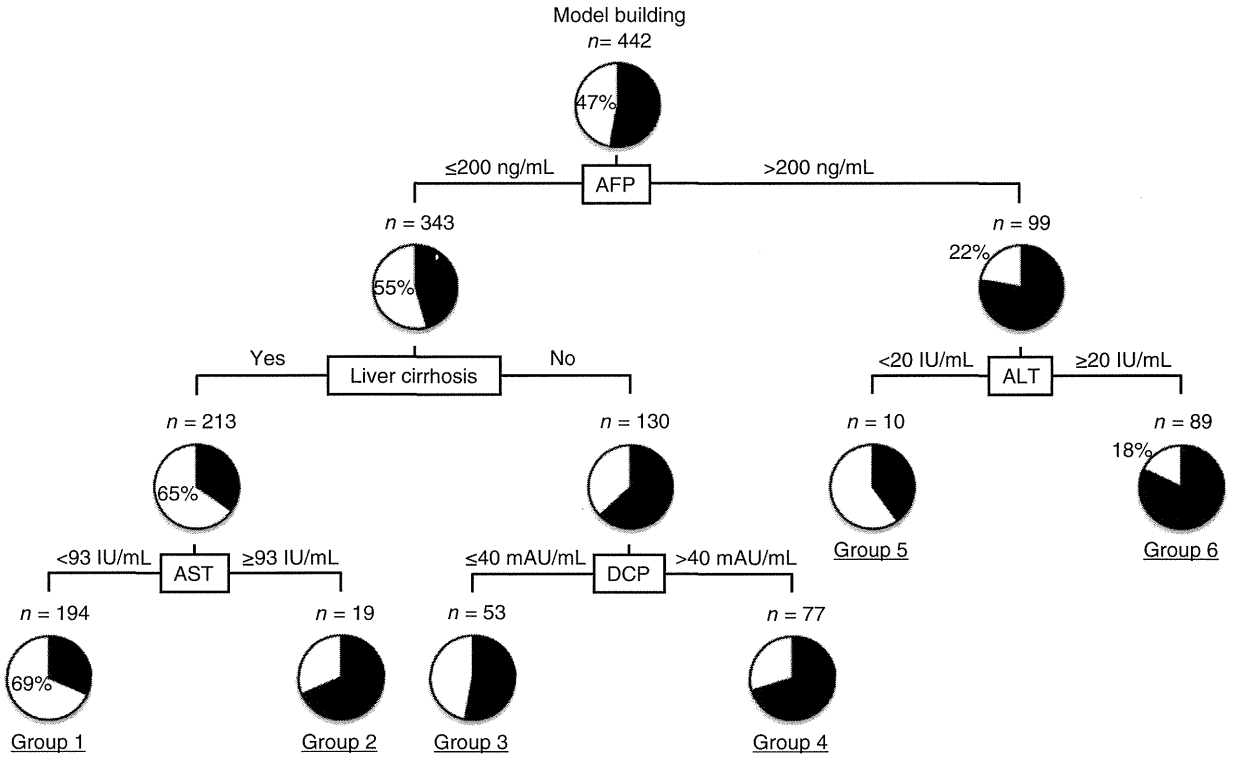

Figure 2 Decision tree algorithm of the variables associated with the Milan criteria. The patients were classified according to the indicated cut-off values of the variables. The pie graphs indicate the percentage of patients with HCC within (white)/beyond the Milan criteria in each group. AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DCP, des-γ-carboxy prothrombin; HCC, hepatocellular carcinoma.

classification. Among the patients with an AFP level of 200 ng/mL or less, diagnosis of liver cirrhosis was used as the variable for the second division. Among the patients with liver cirrhosis, a serum AST level of less than 93 IU/mL was the cut-off value for the third division. Thus, 69% of the patients were within the Milan criteria, when the patients met all of the following conditions: AFP of 200 ng/mL or less; diagnosis of liver cirrhosis; and AST of less than 93 IU/mL (group 1; Fig. 2). On the other hand, only 18% of the patients were within the Milan criteria, when patients showed an AFP level of more than 200 ng/mL and an ALT level of 20 IU/mL or more (group 6; Fig. 2).

There were no significant differences in the patients' characteristics between the training dataset and the test dataset. Prediction error was obtained by applying the results of the decision tree algorithm to the test dataset. The sensitivity (proportion of patients with HCC correctly classified as beyond the Milan criteria) and specificity (proportion of patients with HCC correctly classified as within the Milan criteria) were 72.1% (75/104) and 68.4% (80/117), respectively; the overall prediction error rate was 29.8% (66/221).

DISCUSSION

IN THIS STUDY, we revealed the complex interactions of the risk factors associated with staging of NBNC-HCC using graphical modeling. In addition, we presented a decision tree algorithm to identify clinical feature profiling associated with the staging of NBNC-HCC.

Various factors seem to be intricately related to the progression of NBNC-HCC. In this study, by graphical modeling, we identified six variables directly associated with the Milan criteria: serum AST level; serum ALT level; serum AFP level; serum DCP level; diagnosis of liver cirrhosis; and diagnostic year of HCC. Chronic hepatic inflammation modulates many of the signaling cascades involved in cell proliferation, survival and invasion of