Hepatology Research

Hepatology Research 2019; **49**: 890–901 doi: 10.1111/hepr.13343

Original Article

Japanese periodical nationwide epidemiologic survey of aberrant portal hemodynamics

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Aim: Idiopathic portal hypertension (IPH), extrahepatic portal obstruction (EHO), and Budd–Chiari syndrome (BCS) are characterized by aberrant portal hemodynamics of unknown etiology. The aim of this study was to explore trends in the descriptive epidemiology of these diseases through periodical nationwide surveys.

Methods: Nationwide epidemiologic surveys were undertaken in 1999, 2005, and 2015 using the same protocol. The survey targets were selected from all departments of gastrointestinal medicine, surgery, pediatrics, and pediatric surgery in Japan by stratified random sampling according to the number of beds. We asked each department to complete a mail-back questionnaire on the annual numbers of patients with IPH, EHO, and BCS during the preceding year.

Results: The estimated number of BCS patients increased from 280 (95% confidence interval, 200–360) in 1999 survey to 410 (300–530) in 2015 survey, whereas the number of IPH and EHO patients has remained largely unchanged during the 15 years (IPH was approximately 1000; EHO was approximately 770 in 2015 survey). The mean age at symptom onset was approximately 45 years for IPH, 30 years for EHO, and 40 years for BCS over the past 15 years. Those who described disease aggravation from the time of diagnosis accounted for approximately 10% of IPH, 15% of EHO, and 20% of BCS patients in each of the three surveys.

Conclusions: In Japan, the prevalence of BCS is increasing, while those of IPH and EHO appear to be stable. Clinical characteristics, including prognoses, have remained largely unchanged in the past 15 years.

Key words: Budd–Chiari syndrome, epidemiology, extrahepatic portal obstruction, idiopathic portal hypertension, prevalence

INTRODUCTION

IDIOPATHIC PORTAL HYPERTENSION (IPH), extrahepatic portal obstruction (EHO), and Budd–Chiari syndrome (BCS) are characterized by aberrant portal hemodynamics of unknown etiology. Their clinical features include portal hypertension, bleeding varices, splenomegaly, and pancytopenia. The overall prognosis is considered relatively favorable if the varices can be well controlled.[1,2] However, some patients with hepatic insufficiency or hepatocellular carcinoma have occasionally been reported. According to a report on 65 autopsy cases registered as IPH, progressive hepatic failure was the cause of

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Conflict of interest: The authors have no conflict of interest.

Financial support: This study was supported by an Intractable Diseases, the Health and Labour Sciences Research Grant from the Ministry of Health, Labour and Welfare, Japan.

Received 12 November 2018; revision 18 March 2019; accepted 25 March 2019.

death in 16 cases (25%).[3] However, to our knowledge, as IPH, EHO, and BCS are rare diseases, particularly in the Europe or North America, very few epidemiologic studies have been carried out.

In Japan in 1972, the Ministry of Health, Labour and Welfare established special measures against so-called "intractable diseases", which were defined as rare diseases whose causes and treatments had not yet been determined. Under these measures, the Research Committee on IPH was established in 1975. Extrahepatic portal obstruction and BCS were subsequently added as research subjects, and thus the Research Committee on Aberrant Portal Hemodynamics has been in operation for more than 40 years. When constructing measures to control diseases, it is of the utmost importance to periodically determine the actual disease burden.

Therefore, nationwide epidemiologic surveys on IPH, EHO, and BCS were carried out in 1999, 2005, and 2015 using the same study protocol.[4] The aims of these surveys were to estimate the annual number of patients seeking medical care in Japan and to explore the demographic and clinical characteristics, including prognoses, of these diseases. In the present study, we used data from these three surveys to examine the time trends of prevalence, incidence, and clinical characteristics of these diseases over the past 15 years in Japan.

METHODS

Study participants and measurements

THE NATIONWIDE EPIDEMIOLOGIC surveys were undertaken according to the previously established protocols proposed by the Research Committee on the Epidemiology of Intractable Diseases in Japan.[5] The overall method has been previously described.[4,6–9] The surveys comprised first and second queries. The aim of the first query was to estimate the number of patients who had received treatment for IPH, EHO, and BCS in the preceding year, whereas the aim of the second was to elucidate the patients' demographic and clinical characteristics.

The targets of the first query were selected from all departments of gastrointestinal medicine, surgery, pediatrics, and pediatric surgery dealing with hepatogastrointestinal diseases in Japan by stratified random sampling according to the number of hospital beds. The sampling proportions were as follows: general hospitals with ≤99, 100–199, 200–299, 300–399, 400–499, and 500+ hospital beds were 5, 10, 20, 40, 80, and 100%, respectively; university hospitals were 100%. In addition, for specialized hospitals in which many patients with IPH, EHO, or BCS would have received medical treatment, the sampling proportion was 100%. Selected departments were asked to complete a mail-back questionnaire on the annual numbers of patients with IPH, EHO, or BCS who had been treated at the department in the preceding year. The diagnoses of IPH, EHO, or BCS were based on the criteria proposed by the Research Committee on Aberrant Portal Hemodynamics in Japan.[10] Briefly, IPH is a syndrome of portal hypertension due to the obstruction and stenosis of intrahepatic peripheral portal branches, and exhibits different pathogeneses according to the disease stage. Therefore, diagnosis is made comprehensively based on the findings of laboratory tests, imaging, and pathologies. Extrahepatic portal obstruction is a syndrome that advances to portal hypertension owing to occlusion of the portal vein in the extrahepatic region including the liver hilum. A definite diagnosis is confirmed mostly with reference to imaging findings. Budd–Chiari syndrome is a syndrome that eventually develops portal hypertension owing to obstruction or stenosis of the main trunk of the hepatic vein and the hepatic segment of the inferior vena cava. Confirmed diagnosis is reached mostly with reference to imaging and pathological findings.[10] We mailed a reminder to non-respondents by post at 3 months after the initial mailing.

If a department responded that it had at least one patient in the first query, we sent a second query. The second query was designed to collect data regarding the demographic and clinical characteristics of each treated patient and consisted of the following items: disease name (IPH, EHO, or BCS); sex; date of birth; date of diagnosis; date of symptom onset; family history of IPH, EHO, or BCS; smoking, drinking, and oral contraceptive history before diagnosis; underlying illnesses (i.e. neonatal omphalitis, cholecystitis/cholangitis, hepatitis, phlebothrombosis, collagen disease, blood disease, cancer, and history of splenectomy); clinical symptoms (i.e. esophageal/gastric varices, ascites, splenomegaly, gastrointestinal bleeding, and hepatic encephalopathy), laboratory data and imaging findings (endoscopy, abdominal ultrasonography, computed tomography, magnetic resonance imaging, or abdominal angiography) at the time of diagnosis; invasive treatments for obstruction of BCS (surgery, interventional radiology (IVR), and liver transplantation); date of last observation; disease condition at last observation compared with that at the time of diagnosis (1, deceased; 2, aggravated; 3, unchanged; 4, improved; or 5, recovered); and the cause of death if deceased (gastrointestinal bleeding, hepatic failure, hepatocellular carcinoma, or other). Laboratory data were collected differently between the 1999 and other two surveys. In the 1999 survey, data on the platelet count, albumin, and total bilirubin were collected

as either normal, mild increase or decrease, or severe increase or decrease, whereas in the 2005 and 2015 surveys, these data were collected as measured values. Regarding invasive treatment for obstruction of BCS, we did not collect information on liver transplantation in the 1999 survey. When missing answers or illogical responses were detected, the questionnaire was sent back to the department to be completed or revised.

The surveys in 1999 and 2005 were approved by the ethics review board of the Kyushu University School of Medicine (Fukuoka, Japan), whereas the survey in 2015 was approved by the ethics review board of the Tokyo Medical University (Tokyo, Japan), which was the affiliation of the chair of the Research Committee on Aberrant Portal Hemodynamics.

Statistical analysis

Accounting for the sampling and response proportions in the first query, we estimated the total number of patients with IPH, EHO, or BCS in Japan according to the following formula: the estimated total number of patients = reported number of patients / (sampling proportion × response proportion). Next, we calculated 95% confidence intervals (CIs) with an assumption of multinomial hypergeometric distribution.[5–8] The period prevalence in each year was calculated based on the Japanese population on 1 October each year.[11–13]

The patients' demographic and clinical characteristics were examined by using data from the second query. Age at symptom onset, age at the time of diagnosis, age at last observation, duration from symptom onset to diagnosis, and duration from diagnosis to last observation were calculated from the date of birth, date of symptom onset, date of diagnosis, and date of last observation, respectively. Laboratory data at the time of diagnosis (e.g. platelet count [$\times 10^4/\mu L$], albumin [g/dL], and bilirubin [mg/dL]) were classified into two categories using conventional cut-off points.[14] To apply cut-off points as similar as possible to the data from the 1999 survey, the two categories that deviated from normal were combined in the 1999 survey. In addition, to examine the possible predictors of the implementation of invasive treatments for BCS patients, odds ratios (ORs) and 95% CIs were calculated for each characteristic using the logistic regression model.

All analyses were undertaken using SAS software (version 9.1; SAS Institute, Cary, NC, USA).

RESULTS

In the 2015 survey, 4001 departments were sampled as the survey targets of the first query from 15 115 intended departments in Japan (sampling rate, 26.5%), of which 2442 responded (response rate, 61.0%). We received reports for 388 patients with IPH, 354 with EHO, and 178 with BCS from 299 departments that confirmed they had a patient(s) during the preceding year. Based on these data, we estimated the total number of patients with IPH, EHO, or BCS in Japan to be 1000 (95% CI, 810–1300), 770 (610–930), and 410 (300–530), respectively (Table 1). The period prevalence, per million in 2014 was 7.9 for IPH, 6.1 for EHO, and 3.2 for BCS. Of the patients with available information on the date of diagnosis in the second query, 10% of IPH, 12% of EHO, and 21% of BCS patients were newly diagnosed during 2014. Taken together with the estimated number of patients from the results of the first query, the total number of newly diagnosed patients was estimated to be 100 (1000×0.10) for IPH, 90 (770×0.12) for EHO, and 90 (410×0.21) for BCS. The period incidence, per million in 2014 was 0.8 for IPH, 0.7 for EHO, and 0.7 for BCS. When the same method was used to estimate the numbers of patients from the 1999 and 2005 surveys, the period incidence of IPH and EHO was found to have been decreasing since 1999, whereas the period prevalence was largely unchanged over the past 15 years. However, regarding BCS, compared with the results of the 1999 and 2005 surveys, both the period prevalence and incidence in the 2015 survey appeared to be increasing.

Idiopathic portal hypertension

Table 2 shows the characteristics of patients with IPH from all three surveys. Approximately one-third of the patients were men, and the proportion of confirmed cases was approximately 70%, indicating that the distribution has remained largely unchanged during the past 15 years. Patients with a family history were rare, and the proportion of patients with smoking or drinking habits was the same as that among the general population.[15] Before the diagnosis, the proportion of patients having blood diseases or cancer had increased to 10% in the 2015 survey. Details of cancer prevalence were as follows: 7 breast cancer, 3 hepatocellular carcinoma, 2 colon cancer, 2 thyroid cancer, 2 uterine cancer, 2 ovarian cancer, and one each for the other sites. The mean ages at symptom onset and diagnosis were approximately 45 and 47 years, respectively, meaning that approximately 2 years had passed between symptom onset and diagnosis. The main symptoms were splenomegaly and esophageal varices, which appeared in approximately 80% of patients. Approximately one-third of patients experienced gastrointestinal bleeding at the time of diagnosis. Splenomegaly brought about pancytopenia, with approximately 80% of patients

Table 1 Estimated numbers of patients in Japan with idiopathic portal hypertension (IPH), extrahepatic portal hypertension (EHO), and Budd–Chiari syndrome (BCS) in 1999, 2005, and 2015 epidemiologic surveys

		1999	2005	2015
IPH	No. of total cases (95% CI)	920 (710–1140)	850 (640–1070)	1000 (810–1300)
	Period prevalence, per million	7.3	6.7	7.9
	Proportion of newly diagnosed cases, %	31	21	10
	No. of newly diagnosed cases	290 (220–350)	180 (130–220)	100 (80–130)
	Period incidence, per million	2.3	1.4	0.8
EHO	No. of total cases (95% CI)	720 (540–1040)	450 (340–560)	770 (610–930)
	Period prevalence, per million	5.7	3.5	6.1
	Proportion of newly diagnosed cases, %	38	28	12
	No. of newly diagnosed cases	270 (210–400)	130 (100–160)	90 (70–110)
	Period incidence, per million	2.1	1.0	0.7
BCS	No. of total cases (95% CI)	280 (200–360)	270 (190–360)	410 (300–530)
	Period prevalence, per million	2.2	2.1	3.2
	Proportion of newly diagnosed cases, %	28	6	21
	No. of newly diagnosed cases	80 (60–100)	16 (11–22)	90 (60–110)
	Period incidence, per million	0.6	0.1	0.7

CI, confidence interval.

having a lower platelet count. The disease condition was either aggravated or the patient was deceased for approximately 10% of patients after 10 years compared with the time of diagnosis. Potentially disease-related death (i.e. hepatic failure) accounted for 4 (36%) of the 11 deaths in the 2015 survey.

Extrahepatic portal obstruction

The characteristics of the patients with EHO are shown in Table 3. The male-to-female ratio was approximately 1:1, and most of the patients were confirmed cases. Patients with a family history were rare, and the proportion of patients with smoking or drinking habits was the same as that among the general population.[15] Before the diagnosis, the proportions of patients having cancer were approximately 10% in every survey. According to the 2015 survey, details of cancer prevalence were as follows: 6 hepatocellular carcinoma, 5 pancreatic cancer, 4 cholangiocarcinoma, 2 duodenal cancer, 2 colon cancer, and one each for the other sites, suggesting that some patients showed secondary developed EHO. The mean ages at symptom onset and diagnosis were approximately 30 and 33 years, respectively. The duration between symptom onset and diagnosis was approximately 2 years. The main symptoms were splenomegaly and esophageal varices, which appeared in over 60% of patients. Approximately 60% of patients had anemia or a lower platelet count, and approximately one-third had gastrointestinal bleeding at diagnosis. The disease condition was either aggravated or the patient was deceased for approximately 15% of patients after 10 years compared to the time of diagnosis. Among the 11 deaths in the 2015 survey, three deaths were caused by hepatocellular carcinoma, two deaths were caused by cholangiocarcinoma, and one death was caused by pancreatic cancer, although these six cases with cancer death already had cancer at the time of EHO diagnosis.

Budd–Chiari syndrome

Regarding the characteristics of patients with BCS (Table 4), the proportion of male patients (60%) appeared to be increasing in the 2015 survey. Approximately 90% of patients had a confirmed diagnosis. No patients declared having a family history, but the proportion of patients with a history of smoking or drinking was considered to be higher. Before the diagnosis, the proportions of patients having cancer were approximately 10%. There were six hepatocellular carcinoma cases, and one each for the other sites in the 2015 survey. The mean ages at symptom onset and diagnosis were approximately 38 and 40 years, respectively. The main symptoms were splenomegaly and esophageal varices, which appeared in approximately 60% of patients. Approximately 10% of patients showed gastrointestinal bleeding at the time of diagnosis. In contrast to patients with IPH or EHO, patients with BCS were more likely (approximately 40%) to have a higher bilirubin level. Regarding the obstructive pattern, a mixed type (i.e. both inferior vena cava and hepatic vein) was commonly observed over the past 15 years. During the

Table 2 Characteristics of patients with idiopathic portal hypertension over the past 15 years in Japan

Characteristics		1999 survey ($n = 169$)	2005 survey ($n = 89$)	2015 survey ($n = 279$)
Sex	Male	40/167 (24)	24 (27)	83 (30%)
Confirmation of diagnosis	Confirmed	120/166 (72)	69/88 (78)	203/275 (74%)
Potential causative factors				
Family history	Present	3/142 (2)	0/69 (0)	4/213 (2%)
Smoking habit	Ever	27/162 (17)	10/71 (14)	36/246 (15%)
Drinking habit	Ever	51/164 (31)	17/73 (23)	56/245 (23%)
Oral contraceptives	Ever	0/92 (0)	0/60 (0)	0/228 (0%)
Underlying illnesses				
Neonatal omphalitis	Present	0/81 (0)	1/48 (2)	0/198 (0%)
Cholecystitis/cholangitis	Present	NA	4/69 (6)	7/241 (3%)
Hepatitis	Present	18/149 (12)	7/78 (9)	18/263 (7%)
Phlebothrombosis	Present	NA	1/72 (1)	14/243 (6%)
Collagen diseases	Present	7 (4)	2/84 (2)	18/262 (7%)
Blood diseases	Present	2 (1)	6/84 (7)	25/263 (10%)
Cancer	Present	7 (4)	7/85 (8)	26/265 (10%)
History of splenectomy	Present	24/167 (14)	NA	24/269 (9%)
Age at symptom onset, years†	Mean ± SD	44.7 ± 17.5	46.7 ± 17.0	44.7 ± 19.3
At time of diagnosis				
Age, years‡	Mean ± SD	49.5 ± 16.4	48.6 ± 16.7	47.0 ± 19.1
Duration from symptom onset, years§	Mean ± SD	3.6 ± 7.0	2.4 ± 5.5	1.7 ± 4.0
Clinical symptoms				
Esophageal varices	Present	139/162 (86)	73/84 (87)	184/233 (79%)
Gastric varices	Present	73/152 (48)	44/79 (56)	95/229 (41%)
Ascites	Present	18/169 (11)	12/78 (15)	39/236 (17%)
Splenomegaly	Present	133/169 (79)	70/78 (90)	202/228 (89%)
Anemia	Present	72/169 (43)	40/74 (54)	145/226 (64%)
Gastrointestinal bleeding	Present	57/153 (37)	25/81 (31)	85/247 (34%)
Hepatic encephalopathy	Present	12/169 (7)	1/79 (1)	9/239 (4%)
Laboratory data				
Platelet count, $\times 10^4/\mu L$	<15.8	123/154 (80)	64/74 (86)	189/228 (83%)
Albumin, g/dL	<4.1	62/149 (42)	46/74 (62)	128/219 (58%)
Total bilirubin, mg/dL	≥1.6	42/153 (27)	6/73 (8)	35/224 (16%)
At time of last observation				
Age, years	Mean ± SD	55.9 ± 15.4	57.3 ± 16.4	57.2 ± 18.6
Duration from diagnosis, years‡	Mean ± SD	5.9 ± 6.6	8.0 ± 8.7	10.2 ± 9.0
Disease condition	Recovered	10 (6)	1 (1)	5 (2%)
	Improved	77 (46)	37 (42)	83 (30%)
	Unchanged	64 (38)	41 (46)	159 (58%)
	Aggravated	14 (8)	9 (10)	18 (7%)
	Deceased	2 (1)	1 (1)	11 (4%)
Cause of death	Gastrointestinal bleeding	1	1	0
	Hepatic failure	0	0	4
	Others††	1	0	7

Percentages are shown in parentheses.
†Based on 108, 47, and 171 patients in the 1999, 2005, and 2015 surveys, respectively.
‡Based on 157, 71, and 250 patients in the 1999, 2005, and 2015 surveys, respectively.
§Based on 107, 40, and 161 patients in the 1999, 2005, and 2015 surveys, respectively.
Based on 169, 84, and 279 patients in the 1999, 2005, and 2015 surveys, respectively.
††In the 1999 survey, one patient died from breast cancer. In the 2015 survey, the causes of six deaths were as follows: sepsis ($n = 2$), cholangiocarcinoma ($n = 2$), hemoperitoneum ($n = 1$), interstitial pneumonia ($n = 1$), and unknown cause ($n = 1$).
NA, not applicable; SD, standard deviation.

Table 3 Characteristics of patients with extrahepatic portal hypertension over the past 15 years in Japan

Characteristics		1999 survey ($n = 97$)	2005 survey ($n = 70$)	2015 survey ($n = 211$)
Sex	Male	52 (54)	45 (51)	113 (54)
Confirmation of diagnosis	Confirmed	82 (85)	67 (96)	193/207 (93)
Potential causative factors				
Family history	Present	3/88 (3)	4/66 (6)	3/193 (2)
Smoking habit	Ever	21/92 (23)	11/66 (17)	35/192 (18)
Drinking habit	Ever	35/92 (38)	25/67 (37)	58/193 (30)
Oral contraceptives	Ever	0/38 (0)	0/63 (0)	0/188 (0)
Underlying illnesses				
Neonatal omphalitis	Present	1/54 (2)	0/51 (0)	4/162 (2)
Cholecystitis/cholangitis	Present	NA	10/64 (16)	17/194 (9)
Hepatitis	Present	10/88 (11)	4/69 (6)	16/207 (8)
Phlebothrombosis	Present	NA	2/58 (3)	5/191 (3)
Collagen diseases	Present	1 (1)	0/70 (0)	2/206 (1)
Blood diseases	Present	4 (4)	6/70 (9)	13/207 (6)
Cancer	Present	9 (9)	5/70 (7)	25/206 (12)
History of splenectomy	Present	12/92 (13)	NA	12/205 (6)
Age at symptom onset, years†	Mean ± SD	30.7 ± 26.5	32.0 ± 27.4	25.2 ± 25.3
At time of diagnosis				
Age, years‡	Mean ± SD	37.6 ± 23.9	32.7 ± 26.2	33.1 ± 24.9
Duration from symptom onset, years§	Mean ± SD	2.4 ± 6.2	1.4 ± 3.0	1.8 ± 5.7
Clinical symptoms				
Esophageal varices	Present	69/92 (75)	43/65 (66)	110/164 (67)
Gastric varices	Present	37/90 (41)	31/64 (48)	78/155 (50)
Ascites	Present	18 (19)	17/67 (25)	33/178 (19)
Splenomegaly	Present	56 (58)	42/68 (62)	107/170 (63)
Anemia	Present	33 (34)	37/62 (60)	90/159 (57)
Gastrointestinal bleeding	Present	42/87 (48)	30/69 (43)	67/191 (35)
Hepatic encephalopathy	Present	4 (4)	2/67 (3)	6/179 (3)
Laboratory data				
Platelet count, $\times 10^4/\mu L$	<15.8	48/91 (53)	39/61 (64)	92/160 (58)
Albumin, g/dL	<4.1	35/91 (38)	35/52 (67)	90/156 (58)
Total bilirubin, mg/dL	≥1.6	28/91 (31)	12/61 (20)	26/158 (16)
At time of last observation				
Age, years	Mean ± SD	42.1 ± 22.8	38.7 ± 24.3	43.9 ± 23.1
Duration from diagnosis, years‡	Mean ± SD	4.2 ± 5.5	6.2 ± 7.2	9.8 ± 9.6
Disease condition	Recovered	2 (2)	1 (1)	5 (2)
	Improved	40 (42)	38 (57)	60 (29)
	Unchanged	38 (40)	21 (31)	115 (55)
	Aggravated	4 (4)	3 (4)	19 (9)
	Deceased	12 (13)	4 (6)	11 (5)
Cause of death	Gastrointestinal bleeding	1	1	1
	Hepatic failure	7	1	3
	Hepatocellular carcinoma	0	0	3
	Others††	4	2	4

Percentages are shown in parentheses.
†Based on 53, 55, and 122 patients in the 1999, 2005, and 2015 surveys, respectively.
‡Based on 92, 61, and 189 patients in the 1999, 2005, and 2015 surveys, respectively.
§Based on 52, 53, and 114 patients in the 1999, 2005, and 2015 surveys, respectively.
Based on 97, 65, and 210 patients in the 1999, 2005, and 2015 surveys, respectively.
††In the 1999 survey, the causes of four deaths were as follows: cancer ($n = 1$), stroke ($n = 1$), and pulmonary hypertension ($n = 2$). In the 2005 survey, one patient died from pancreatic cancer and one from thrombotic thrombocytopenic purpura and sepsis. In the 2015 survey, the causes of four deaths were as follows: cholangiocarcinoma ($n = 2$), pancreatic cancer ($n = 1$), and unknown cause ($n = 1$).
NA, not applicable; SD, standard deviation.

Table 4 Characteristics of patients with Budd–Chiari syndrome over the past 15 years in Japan

Characteristics		1999 survey ($n = 44$)	2005 survey ($n = 33$)	2015 survey ($n = 112$)
Sex	Male	17 (39)	19 (22)	67 (60)
Confirmation of diagnosis	Confirmed	44 (100)	31 (94)	96/111 (86)
Potential causative factors				
Family history	Present	0/40 (0)	0/32 (0)	0/94 (0)
Smoking habit	Ever	17 (39)	6/31 (19)	37/93 (40)
Drinking habit	Ever	16 (36)	7/31 (23)	42/91 (46)
Oral contraceptives	Ever	0/20 (0)	1/30 (3)	2/88 (2)
Underlying illnesses				
Neonatal omphalitis	Present	0/17 (0)	0/24 (0)	0/68 (0)
Cholecystitis/cholangitis	Present	NA	0/31 (0)	2/88 (2)
Hepatitis	Present	4/41 (10)	1/32 (3)	11/100 (11)
Phlebothrombosis	Present	NA	1/32 (3)	14/92 (15)
Collagen diseases	Present	2 (5)	0/32 (0)	5/101 (5)
Blood diseases	Present	1 (2)	1/31 (3)	6/103 (6)
Cancer	Present	5 (11)	0/32 (0)	9/101 (9)
History of splenectomy	Present	1 (2)	NA	1/107 (1)
Age at symptom onset, years†	Mean ± SD	43.0 ± 17.9	39.0 ± 15.8	38.3 ± 15.6
At time of diagnosis				
Age, years‡	Mean ± SD	48.6 ± 18.5	41.7 ± 16.8	40.5 ± 16.0
Duration from symptom onset, years§	Mean ± SD	2.0 ± 3.6	1.6 ± 2.6	1.5 ± 3.9
Clinical symptoms				
Esophageal varices	Present	36/41 (88)	21/29 (72)	52/91 (57)
Gastric varices	Present	9/40 (23)	7/28 (25)	21/90 (23)
Ascites	Present	11/43 (26)	13/31 (42)	41/99 (41)
Splenomegaly	Present	22/43 (51)	23/29 (79)	59/93 (63)
Anemia	Present	6/43 (14)	4/30 (13)	34/88 (39)
Gastrointestinal bleeding	Present	4/38 (11)	2/29 (7)	12/105 (11)
Hepatic encephalopathy	Present	0/44 (0)	3/30 (10)	8/105 (8)
Laboratory data				
Platelet count, $\times 10^4/\mu L$	<15.8	31/41 (76)	22/30 (73)	57/88 (65)
Albumin, g/dL	<4.1	17/38 (45)	19/28 (68)	52/87 (60)
Total bilirubin, mg/dL	≥1.6	21/40 (53)	12/29 (41)	34/88 (39)
Type of obstructive pattern				
Inferior vena cava (isolated)		17/38 (45)	7/29 (24)	16/78 (21)
Hepatic vein (isolated)		1/38 (3)	4/29 (14)	17/78 (22)
Both inferior vena cava and hepatic vein		20/38 (53)	18/29 (62)	45/78 (58)
Treatment for obstruction				
Liver transplantation		NA	1/33 (3)	7/109 (6)
Surgery other than liver transplantation		20/42 (48)	5/33 (15)	8/109 (7)
Interventional radiology		5/42 (12)	13/33 (39)	35/109 (32)
At time of last observation				
Age, years	Mean ± SD	55.3 ± 16.2	48.5 ± 17.8	50.4 ± 16.5
Duration from diagnosis, years‡	Mean ± SD	5.8 ± 5.7	6.7 ± 5.1	9.5 ± 8.8
Disease condition	Recovered	2 (5)	1 (3)	2 (2)
	Improved	23 (52)	15 (45)	34 (31)
	Unchanged	14 (32)	10 (30)	51 (46)
	Aggravated	2 (5)	5 (15)	14 (13)
	Deceased	3 (7)	2 (6)	10 (9)
Cause of death	Gastrointestinal bleeding	0	0	1

(*Continues*)

Table 4. (Continued)

Characteristics		1999 survey ($n = 44$)	2005 survey ($n = 33$)	2015 survey ($n = 112$)
	Hepatic failure	1	1	4
	Hepatocellular carcinoma	1	0	1
	Others††	0	1	4

Percentages are shown in parentheses.
†Based on 28, 21, and 67 patients in the 1999, 2005, and 2015 surveys, respectively.
‡Based on 41, 31, and 99 patients in the 1999, 2005, and 2015 surveys, respectively.
§Based on 27, 21, and 65 patients in the 1999, 2005, and 2015 surveys, respectively.
Based on 44, 31, and 111 patients in the 1999, 2005, and 2015 surveys, respectively.
††In the 2005 survey, one patient died from an unknown cause. In the 2015 survey, the causes of four deaths were as follows: stroke ($n = 2$), colon cancer ($n = 1$), and pneumonia ($n = 1$).
NA, not applicable; SD, standard deviation.

disease course, approximately half of the patients received invasive treatments. Approximately 20% of patients showed an aggravated disease condition after 10 years compared with the time of diagnosis. Potentially disease-related death (i.e. gastrointestinal bleeding, hepatic failure, or hepatocellular carcinoma) accounted for 6 (60%) of the 10 deaths in the 2015 survey. One death caused by hepatocellular carcinoma did not have cancer at the time of BCS diagnosis. Patients who had received invasive treatments were more likely to show "recovered" or "improved" disease condition than were those who had not (68% vs. 35% in the 1999 survey, 74% vs. 14% in the 2005 survey, and 58% vs. 10% in the 2015 survey).

As for the potential predictors of the implementation of invasive treatments for BCS patients (Table 5), confirmed cases (OR = 3.45, $P = 0.08$), those with longer duration from symptom onset to BCS diagnosis (OR = 9.30, $P < 0.01$), and those with ascites (OR = 2.60, $P = 0.03$), splenomegaly (OR = 2.63, $P = 0.06$), anemia (OR = 2.60, $P = 0.09$), or lower albumin level (OR = 2.37, $P = 0.099$) at the time of diagnosis tended to receive invasive treatments during their disease course. Although the same analysis was carried out using data from the 1999 and 2005 survey, the number of patients were too limited to obtain meaningful results.

DISCUSSION

THE RESULTS OF the present study suggest that the prevalence of BCS is increasing, whereas those of IPH and EHO have remained largely unchanged over the past 15 years. To our knowledge, no national data regarding the incidence and prevalence of IPH have been published, and thus, we are unable to compare our findings with any other external evidence. Regarding EHO, one study involving Israeli children reported that the incidence was 0.72 per million,[16] which is similar to that in the present study. As for BCS, the incidence and prevalence of BCS in Japan is smaller than those in Italy[17] and South Korea,[18] but is similar to those in Sweden, Denmark, and France.[19,20] In Japan, the number of certificates issued for specific disease treatment of BCS increased from 60 in 1998 to 293 in 2014.[21] In addition, a Japanese nationwide survey undertaken in 1989 reported a prevalence of 2.4 per million and an incidence of 0.2 per million.[22] Therefore, even compared with the results from the 1989 study, the incidence and prevalence of BCS has been increasing.

The reason the number of BCS patients has been increasing in Japan remains unclear. Although the diagnostic criteria has not largely changed in this 15-year period,[10] imaging techniques such as ultrasonography, computed tomography, magnetic resonance imaging, and angiography has been advancing, which might contribute to early diagnosis of BCS. In addition, IVR has become popular as a treatment for obstruction sites, so treatment less invasive than surgery can be chosen. In the present study, however, the prognosis was found to have remained largely unchanged over the study period, suggesting that the accumulation of incident rather than prevalent cases might have influenced the increased number of patients. However, we did not collect information about the imaging method used to reach the diagnosis. Thus, it seems sensible to have reservations about the relationship between the advancing diagnostic techniques and the number of patients.

The causal factors of aberrant portal hemodynamics, including BCS, have yet to be clarified. Previous studies have suggested that potential causative factors are

Table 5 Association between characteristics at diagnosis and the implementation of invasive treatments for obstruction of Budd–Chiari syndrome as potential predictors of invasive treatments: 2015 survey, Japan

		Invasive treatments	Univariate	Multivariate†
Characteristic		*n*/*N* (%)	OR (95% CI)	OR (95% CI)
Total		50/109 (46)		
Sex	Male	29/65 (45)	1.00	1.00
	Female	21/44 (48)	1.13 (0.53–2.44)	1.14 (0.49–2.65)
Confirmation of diagnosis	Not confirmed	3/15 (20)	1.00	1.00
	Confirmed	46/93 (49)	3.92 (1.04–14.8)	3.45 (0.87–13.7)
Age at diagnosis, years	<40	21/51 (49)	1.00	1.00
	40+	18/47 (38)	0.65 (0.29–1.44)	0.60 (0.26–1.39)
Duration from symptom onset, years	<1.0	17/46 (37)	1.00	1.00
	1.0+	14/18 (78)	5.97 (1.69–21.1)	9.30 (2.14–40.4)
Clinical symptoms at diagnosis				
Ascites	Absent	22/57 (39)	1.00	1.00
	Present	24/41 (59)	2.25 (0.99–5.09)	2.60 (1.08–6.27)
Splenomegaly	Absent	9/34 (26)	1.00	1.00
	Present	30/58 (52)	2.98 (1.19–7.47)	2.63 (0.96–7.19)
Anemia	Absent	21/53 (40)	1.00	1.00
	Present	18/34 (53)	1.71 (0.72–4.09)	2.60 (0.88–7.70)
Laboratory data				
Albumin, g/dL	<4.1	26/51 (51)	1.99 (0.82–4.84)	2.37 (0.85–6.60)
	4.1+	12/35 (34)	1.00	1.00
Type of obstructive pattern				
Inferior vena cava (isolated)		6/16 (38)	1.00	1.00
Hepatic vein (isolated)		5/17 (29)	0.69 (0.16–2.97)	0.42 (0.08–2.32)
Both inferior vena cava and hepatic vein		26/44 (59)	2.41 (0.74–7.81)	1.84 (0.46–7.38)

†Adjusted for sex, confirmation of diagnosis, and age at diagnosis.
CI, confidence interval; OR, odds ratio.

immunological disorders for IPH,[23] hyperhomocysteinemia, antiphospholipid antibodies, and myeloproliferative disorders for EHO,[24] and myeloproliferative disorders, thrombophilic factors, and oral contraceptives for BCS.[20] However, these studies also pointed out that approximately one-third of patients had no risk factors.[20,24] In the present study, some IPH patients had blood diseases, cancer, collagen diseases, or phlebothrombosis, some EHO patients had cancer, blood diseases, or cholecystitis/cholangitis, and some BCS patients had phlebothrombosis, cancer, or blood diseases, which suggested that these underlying conditions might be associated with the disease etiology. However, patients without these underlying conditions accounted for 68% of IPH, 64% of EHO, and 65% of BCS patients, suggesting that the etiology in most of the patients is unknown. Additionally, BCS patients in the 2015 survey were more likely to smoke (40%) and drink (46%), the proportions of which were higher than those of the general population in Japan. According to the National Health and Nutrition Examination Survey in 2015, 30.1% of men and 7.9% of women in Japan had a smoking habit, whereas 13.9% of men and 8.1% of women had a drinking habit.[15] Therefore, smoking and drinking habits might affect the disease etiology of BCS. However, this is speculative in the present study based on only one case series study. Thus, further studies from the perspective of analytic epidemiology (i.e. a case–control study) are needed to clarify the risk factors for the development of these diseases.

The clinical characteristics of IPH, EHO, and BCS, including age at symptom onset, age at diagnosis, and symptoms and laboratory data at the time of diagnosis, remained largely unchanged over the past 15 years. The main symptoms were splenomegaly and esophageal varices, which were observed in approximately 80–90% of IPH, 60–70% of EHO, and 60% of BCS patients. In addition, a relevant proportion of patients showed pancytopenia owing to splenomegaly and anemia owing to gastrointestinal bleeding. Less than 10% of patients had symptoms of hepatic failure, including hepatic

encephalopathy, at the time of diagnosis. These clinical characteristics are comparable to those reported in a previous nationwide survey in 1989 in Japan[22,25] and studies from other countries.[23,26,27] Regarding BCS, the mixed type obstructive pattern was commonly observed in the present study, whereas it accounted for approximately 30% in an Indian study[28] and 24% in a Chinese study.[29] These findings suggest that different obstructive patterns might be the result of lifestyle or racial differences.

Regarding the prognosis, approximately 10% of IPH, 15% of EHO, and 20% of BCS patients declared that their disease condition was aggravated compared with that at the time of diagnosis, and these proportions have remained largely unchanged over the past 15 years. Although the present study could not investigate survival rates because of its cross-sectional design, previous cohort studies have suggested that the 10-year survival rate was approximately 80% for IPH[23,30] and approximately 70% for EHO.[31] Taken together, the prognoses of IPH and EHO are relatively favorable. However, as some factors were reported to be related to the prognosis of IPH (i.e. presence of esophageal varices,[4,32] hepatic encephalopathy,[4] and portal vein thrombosis[33]), controlling these conditions is important for their clinical management. In addition, the reported 10-year survival rate among BCS patients has been reported to range between 17% and 74%.[20,34,35] The lowest survival was reported in a study involving patients diagnosed from 1986 to 2003.[19] In general, the survival rate has been increasing as a result of recent advances in therapeutic techniques. One review indicated that the survival rates from studies undertaken after 2006 were as high as 90% at 1 year, 83% at 5 years, and 72% at 10 years.[2] Therefore, the prognosis of BCS is improving. However, as survival among BCS patients with portal vein or splenomesenteric vein thrombosis tend to be worse,[36] more careful management might be needed for these patients.

Patients with BCS have been reported to be more likely to develop hepatocellular carcinoma.[37] According to a recent systematic review, the pooled prevalence of hepatocellular carcinoma was 17.6% (95% CI, 10.1–26.7%) in BCS patients and 15.4% (6.8–26.7%) in BCS patients without viral hepatitis.[38] The survival rate is reportedly worse in BCS patients with hepatocellular carcinoma,[35] and thus, early detection and treatment of hepatocellular carcinoma is an important issue for the clinical management of BCS. Although the present study also showed that one patient died from hepatocellular carcinoma, the main cause of death was hepatic failure; additionally, one patient died from gastrointestinal bleeding (Table 4). Taken together, to improve the prognosis of BCS patients, in addition to controlling esophageal/gastric varices, it is important to carry out periodical laboratory examinations to screen for hepatic failure and periodical imaging examinations to screen for hepatocellular carcinoma.

In general, it has been considered that IPH and EHO patients carry a good prognosis and have a very low risk of progression to hepatocellular carcinoma.[39] In the present study, no death caused by hepatocellular carcinoma was reported among IPH patients in the three surveys, whereas three deaths caused by hepatocellular carcinoma were reported among the EHO patients. However, these three EHO patients had already been diagnosed with hepatocellular carcinoma at the time of EHO diagnosis, suggesting that these patients developed secondary EHO resulting from the hepatocellular carcinoma, rather than developing hepatocellular carcinoma during the disease course of EHO.

As for the treatment of BCS, IVR had become the main treatment by the 2015 survey, and it is expected to be more popular in the future, as it is less invasive than surgery. However, those receiving invasive treatments for the obstruction of BCS, whether IVR, surgery, or liver transplantation, are more likely to show a better prognosis than those who had not. According to the detailed analysis of data from the 2015 survey, confirmed cases, those with longer duration from symptom onset, and those with ascites, splenomegaly, anemia, and lower albumin levels at the time of diagnosis tended to receive invasive treatments during their disease course. Although this evaluation using only one survey might require care in terms of its generalizability, this result would be potentially useful when considering the implementation of invasive treatments for BCS patients.

As the present study has a cross-sectional design based on only one case series study, the following limitations should be noted. First, as the present study targeted IPH, EHO, and BCS cases at a particular time point, patients who died because of rapid disease progression were less likely to be included, which resulted in most of the participants being milder cases (selection bias). However, most of the results were compatible with those of previous studies, suggesting that any effect of a potential selection bias was relatively small. Second, a cross-sectional study design is not generally capable of revealing the disease prognosis; thus, we could not undertake a survival analysis. In the present study, based on the physicians' reports, a potential prognostic indicator was used as the disease condition and was compared with that at the time of diagnosis. We believe that such information must be provided after comparing clinical data at the present state with those at the time of diagnosis; however, this information might be

subjective. Finally, as the results regarding the patients' clinical characteristics were based on pre-existing data from their medical records, the data that were unavailable resulted in missing information for each variable. Therefore, clinical characteristics that have a lesser degree of missing information would be more reliable.

In conclusion, the results of the present study suggest that the prevalence of BCS is increasing in Japan, whereas the prevalence of IPH and EHO appear to have been relatively stable over the past 15 years. Furthermore, the patients' clinical characteristics, including main symptoms and prognoses, have remained largely unchanged.

ACKNOWLEDGMENTS

THE AUTHORS WISH to thank the doctors and staff of all departments that participated in the Japanese nationwide epidemiological survey for their kind cooperation. This study was supported by an Intractable Diseases, the Health and Labour Sciences Research Grant from the Ministry of Health, Labour and Welfare, Japan.

REFERENCES

1 Harmanci O, Bayraktar Y. Clinical characteristics of idiopathic portal hypertension. *World J Gastroenterol* 2007; **13**: 1906–11.
2 Qi X, Ren W, Wang Y, Guo X, Fan D. Survival and prognostic indicators of Budd–Chiari syndrome: a systematic review of 79 studies. *Expert Rev Gastroenterol Hepatol* 2015; **9**: 865–75.
3 Sawada S, Sato Y, Aoyama H, Harada K, Nakanuma Y. Pathological study of idiopathic portal hypertension with an emphasis on cause of death based on records of annuals of pathological autopsy cases in Japan. *J Gastroenterol Hepatol* 2007; **22**: 204–9.
4 Murai Y, Ohfuji S, Fukushima W *et al.* Prognostic factors in patients with idiopathic portal hypertension: two Japanese nationwide epidemiological surveys in 1999 and 2005. *Hepatol Res* 2012; **42**: 1211–20.
5 Nakamura Y, the Study Group on Epidemiologic Research for Intractable Diseases. A manual of a nationwide epidemiological survey for estimating the number of patients and assessing clinico-epidemiological characteristics of patients with intractable diseases (3rd edition) [in Japanese]. 2017. Available at: http://www.jichi.ac.jp/dph/nanbyou/manual_2017.pdf. Accessed 15 February, 2019.
6 Hashimoto S, Fukutomi K, Nagai M *et al.* A note on methods for estimating the number of patients in the nationwide epidemiological survey on intractable diseases [in Japanese. *Nihon Koshu Eisei Zasshi* 1990; **37**: 768–74.
7 Hashimoto S, Fukutomi K, Nagai M *et al.* A method of interval estimation for number of patients in the nationwide epidemiological survey on intractable diseases [in Japanese. *Nihon Koshu Eisei Zasshi* 1991; **38**: 880–3.
8 Nakamura Y, Matsumoto T, Tamakoshi A *et al.* Prevalence of idiopathic hypoparathyroidism and pseudohypoparathyroidism in Japan. *J Epidemiol* 2000; **10**: 29–33.
9 Fukushima W, Fujioka M, Kubo T, Tamakoshi A, Nagai M, Hirota Y. Nationwide epidemiologic survey of idiopathic osteonecrosis of the femoral head. *Clin Orthop Relat Res* 2010; **468**: 2715–24.
10 The Aberrant Portal Hemodynamics Study Group supported by the Ministry of Health. Labor and Welfare of Japan. Diagnosis and treatment guidelines for aberrant portal hemodynamics. *Hepatol Res* 2017; **47**: 373–86.
11 Population Estimates, Statistics Bureau of the Ministry of Internal Affairs and Communications. Available at: https://www.e-stat.go.jp/stat-search/files?page=1&layout=datalist&lid=000001010887. Accessed 31 January, 2018.
12 Population Estimates, Statistics Bureau of the Ministry of Internal Affairs and Communications. Available at: http://www.stat.go.jp/data/jinsui/2004np/index.htm. Accessed 31 January, 2018.
13 Population Estimates, Statistics Bureau of the Ministry of Internal Affairs and Communications. Available at: http://www.stat.go.jp/data/jinsui/2014np/. Accessed 31 January, 2018.
14 Website of SRL General Testing Information. Available at: http://test-guide.srl.info/. Accessed 1 February, 2017.
15 Ministry of Health, Labour and Welfare. The results of National Health and Nutrition Examination Survey in 2015 [in Japanese]. Available at: http://www.mhlw.go.jp/file/04-Houdouhappyou-10904750-Kenkoukyoku-Gantaisakuken-kouzoushinka/kekkagaiyou.pdf. Accessed 31 January, 2018.
16 Weiss B, Shteyer E, Vivante A *et al.* Etiology and long-term outcome of extrahepatic portal vein obstruction in children. *World J Gastroenterol* 2010; **16**: 4968–72.
17 Ageno W, Dentali F, Pomero F *et al.* Incidence rates and case fatality rates of portal vein thrombosis and Budd–Chiari syndrome. *Thromb Haemost* 2017; **117**: 794–800.
18 Ki M, Choi HY, Kim KA, Kim BH, Jang ES, Jeong SH. Incidence, prevalence and complications of Budd–Chiari syndrome in South Korea: a nationwide, population-based study. *Liver Int* 2016; **36**: 1067–73.
19 Rajani R, Almer S. Incidence and prevalence rates in Budd–Chiari syndrome. *Gut* 2009; **58**: 889.
20 Rajani R, Melin T, Bjornsson E *et al.* Budd–Chiari syndrome in Sweden: epidemiology, clinical characteristics and survival – an 18-year experience. *Liver Int* 2009; **29**: 253–9.
21 Japan Intractable Diseases Information Center. The number of certificates issued for specific disease treatment. Available at: http://www.nanbyou.or.jp/entry/1356. Accessed 7 March, 2019.
22 Okuda H, Yamagata H, Obata H *et al.* Epidemiological and clinical features of Budd–Chiari syndrome in Japan. *J Hepatol* 1995; **22**: 1–9.
23 Siramolpiwat S, Seijo S, Miquel R *et al.* Idiopathic portal hypertension: natural history and long-term outcome. *Hepatology* 2014; **59**: 2276–85.

24 Amarapurkar P, Bhatt N, Patel N, Amarapurkar D. Primary extrahepatic portal vein obstruction in adults: a single center experience. *Indian J Gastroenterol* 2014; **33**: 19–22.
25 Okudaira M, Ohbu M, Okuda K. Idiopathic portal hypertension and its pathology. *Semin Liver Dis* 2002; **22**: 59–71.
26 Dhiman RK, Chawla Y, Vasishta RK *et al*. Non-cirrhotic portal fibrosis (idiomathic portal hypertension): experience with 151 patients and a review of the literature. *J Gastroenterol Hepatol* 2002; **17**: 6–16.
27 Boyer JL, Sen Gupta KP, Biswas SK *et al*. Idiopathic portal hypertension: comparison with the portal hypertension of cirrhosis and extrahepatic portal vein obstruction. *Ann Intern Med* 1967; **66**: 41–68.
28 De BK, De KK, Sen S *et al*. Etiology based prevalence of Budd–Chiari syndrome in eastern India. *J Assoc Physicians India* 2000; **48**: 800–3.
29 Li G, Huang Y, Tang S *et al*. A single-center retrospective study: clinical features of different types of Budd–Chiari syndrome in Chinese patients in the Hubei area. *Vascular* 2018; **26**: 80–9.
30 Ohashi K, Kojima K, Fukazawa M, Beppu T, Futagawa S. Long-term prognosis of non-shunt operation for idiopathic portal hypertension. *J Gastroenterol* 1998; **33**: 241–6.
31 Sekimoto T, Maruyama H, Kobayashi K *et al*. Well-tolerated portal hypertension and favorable prognosis in adult patients with extrahepatic portal vein obstruction in Japan. *Hepatol Res* 2016; **46**: 505–13.
32 Ichimura S, Sasaki R, Takemura Y *et al*. The prognosis of idiopathic portal hypertension in Japan. *Intern Med* 1993; **32**: 441–4.
33 Matsutani S, Maruyama H, Akiike T *et al*. Study of portal vein thrombosis in patients with idiopathic portal hypertension in Japan. *Liver Int* 2005; **25**: 978–83.
34 Montano-Loza AJ, Tandon P, Kneteman N *et al*. Rotterdam score predicts early mortality in Budd–Chiari syndrome, and surgical shunting prolongs transplant-free survival. *Aliment Pharmacol Ther* 2009; **30**: 1060–9.
35 Park H, Yoon JY, Park KH *et al*. Hepatocellular carcinoma in Budd–Chiari syndrome: a single center experience with long-term follow-up in South Korea. *World J Gastroenterol* 2012; **18**: 1946–52.
36 Darwish Murad S, Valla DC, de Groen PC *et al*. Pathogenesis and treatment of Budd–Chiari syndrome combined with portal vein thrombosis. *Am J Gastroenterol* 2006; **101**: 83–90.
37 Moucari R, Rautou PE, Cazals-Hatem D *et al*. Hepatocellular carcinoma in Budd–Chiari syndrome: characteristics and risk factors. *Gut* 2008; **57**: 828–35.
38 Ren W, Qi X, Yang Z, Han G, Fan D. Prevalence and risk factors of hepatocellular carcinoma in Budd–Chiari syndrome: a systematic review. *Eur J Gastroenterol Hepatol* 2013; **25**: 830–41.
39 Okuda K, Nakashima T, Kojiro M, Kondo Y, Wada K. Hepatocellular carcinoma without cirrhosis in Japanese patients. *Gastroenterology* 1989; **97**: 140–6.