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MINIREVIEWS

Hepatectomy for hepatocellular carcinoma with portal vein tumor thrombus

Toshiya Kamiyama, Tatsuhiko Kakisaka, Tatsuya Orimo, Kenji Wakayama

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Abstract

Despite surgical removal of tumors with portal vein tumor thrombus (PVTT) in hepatocellular carcinoma (HCC) patients, early recurrence tends to occur, and overall survival (OS) periods remain extremely short. The role that hepatectomy may play in long-term survival for HCC with PVTT has not been established. The operative mortality of hepatectomy for HCC with PVTT has also not been reviewed. Hence, we reviewed recent literature to assess these parameters. The OS of patients who received hepatectomy in conjunction with multidisciplinary treatment tended to be superior to that of patients who did not. Multidisciplinary treatments included the following: preoperative radiotherapy on PVTT; preoperative transarterial chemoembolization (TACE); subcutaneous administration of interferon-alpha (IFN-α) and intra-arterial infusion of 5-fluorouracil (5-FU) with infusion chemotherapy in the affected hepatic artery; cisplatin, doxorubicin and 5-FU locally administered in the portal vein; and subcutaneous injection of IFN-α, adjuvant chemotherapy (5-FU + Adriamycin) administration *via* the portal vein with postoperative TACE, percutaneous isolated hepatic perfusion and hepatic artery infusion and/or portal vein chemotherapy. The highest reported rate of operative mortality was 9.3%. In conclusion, hepatectomy for patients affected by HCC with PVTT is safe, has low mortality and might prolong survival in conjunction with multidisciplinary treatment.

Key words: Hepatocellular carcinoma; Portal vein tumor thrombus; Hepatectomy; Multidisciplinary treatment; Operative mortality

Core tip: Hepatocellular carcinoma (HCC) is characterized by early formation of portal vein tumor thrombus (PVTT). Even after surgical removal of the tumors with PVTT in HCC patients, early recurrence has been frequently

reported due to intrahepatic metastasis from PVTT. There have been reports of long-term survival after hepatectomy in patients with macroscopic PVTT. The operative mortality of major hepatectomy for HCC patients with macroscopic PVTT has not been well documented or discussed. To this end, we reviewed recent literature on the significance of hepatectomy in HCC with macroscopic PVTT with respect to the long-term survival and mortality.

Kamiyama T, Kakisaka T, Orimo T, Wakayama K. Hepatectomy for hepatocellular carcinoma with portal vein tumor thrombus. *World J Hepatol* 2017; 9(36): 1296-1304 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i36/1296.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i36.1296

INTRODUCTION

Hepatocellular carcinoma (HCC) is characterized by early formation of portal vein tumor thrombus (PVTT)[1]. An important prognostic factor and predictor for HCC recurrence is PVTT[2,3]. The effectiveness of transarterial chemoembolization (TACE) for HCC with PVTT remains unclear[4,5] though TACE is included in the treatment for HCC with tumor thrombus in the main portal branch[6]. However, it was suggested that hepatic arterial infusion chemotherapy might be a hopeful approach[7,8]. Because the median survival for untreated patients with PVTT is only 2.7 mo, this suggestion is especially relevant[9]. Hepatectomy for advanced HCC with removal of PVTT might also warrant consideration as an adjuvant treatment though it is usually performed as an emergency operation to avoid lethal complications[10]. Early recurrence has been reported in many cases due to intrahepatic metastasis from PVTT[11] even after tumors with PVTT in HCC patients was surgically removed. On the other hand, there have been reports of long-term survival after hepatectomy in patients with macroscopic portal invasion[12,13], but whether this treatment is optimal for patients with major PVTT remains controversial. Moreover, the operative mortality of major hepatectomy for HCC with macroscopic PVTT has not been well documented and reviewed. Therefore, we review literature published after January 2000 about the significance of hepatectomy in HCC with macroscopic PVTT with respect to long-term survival and mortality.

SURGICAL GUIDELINES FOR RESECTION IN HCC WITH PVTT

Because the cancer has already disseminated at this stage, leading to high rates of recurrence, hepatectomy for HCC with portal invasion is not recommended in the barcelona clinic liver cancer (BCLC) staging and treatment strategy. Portal invasion is associated with the development of metastatic nests, with higher incidence in tumors exhibiting microvascular invasion and/or satellite lesions[14].

According to the BCLC staging classification, sorafenib is the treatment of choice for HCC with macroscopic portal invasion (BCLC stage C). The efficacy of sorafenib in the treatment of advanced HCC was recently confirmed by the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial. In that report, the median overall survival was 7.9 mo in the placebo group compared to 10.7 mo in the sorafenib group. The benefit of sorafenib was consistent in the pre-specified stratification groups that included patients with the worst prognosis, such as those with macroscopic vascular invasion[15]. According to the BCLC staging classification, hepatectomy is contraindicated in HCC with Vp3 (tumor thrombus in the first branch of the portal vein) or Vp4 (tumor thrombus extension to the trunk or to the opposite side branch of the portal vein) and should only be performed in patients with small single tumors without signs of portal hypertension or hyperbilirubinemia. On the other hand, the proposed treatment for HCC with minimal portal invasion, such as Vp1 (tumor thrombus distal to the second branches of the portal vein) and Vp2 (tumor thrombus in the second branches of the portal vein), is hepatectmy combined with TACE in the Japan Society of Hepatology (JSH) algorithm[16]. Indeed, when hepatectomy was performed in selected patients affected by HCC with macroscopic PVTT, in combination with either postoperative arterial infusion therapy or preoperative TACE, long-term survival was achieved[13,17].

In the 17th Nationwide Follow-up Survey of Primary Liver Cancer report in Japan, it was stated that the survival rates of 976 hepatectomized HCC patients with Vp3 or Vp4 were 50.4%, 25.8% and 18.4% at 1, 3 and 5 years, respectively[1].

HEPATECTOMY WITH MULTIDISCIPLINARY TREATMENT FOR PVTT

The prognosis of the HCC patients with PVTT in the first branch or main trunk is very poor, with a median survival of only 2.7 mo if appropriate treatments are not employed[9]. However, in the present literature search, we identified instances of long-term survival after hepatectomy. The range of overall survival (OS) rates for patients who received hepatectomy without multidisciplinary treatment were from 14.2% to 86.5% at 1 year, 0% to 60.4% at 3 years and 0 to 33.3% at 5 years (Table 1). On the other hand, the range of the OS rates for patients who received hepatectomy with multidisciplinary treatment were from 0% to 100% at 1 year, 14.0% to 74.0% at 3 years and 21.5% to 42.0% at 5 years (Table 1). From these data, we can see that the OS rates of patients who received hepatectomy with multidisciplinary treatment tended to be superior to those of patients who did not receive multidisciplinary treatment. This favorable

Table 1 Surgical outcome of hepatectomy for hepatocellular carcinoma patients with portal vein thrombus

Ref.	Vp type	Patients	Child-Pugh A (%)	HBV (%)	OS, 1 yr (%)	OS, 3 yr (%)	OS, 5 yr (%)	Treatment
Ohkubo *et al*[11] 2000	Vp234	47	91.5	42.6	53.9	33.2	23.9	
Minagawa *et al*[13] 2001	Vp234	18	NS	44.4	82	42	42	Preop TACE
Fan *et al*[26] 2003	Vp34	19	78.9	NS	14.2	0	0	
	Vp34	64	78.1	NS	37.6	14	NS	Postop PVI HAI
Capussotti *et al*[42] 2004	Vp234	13	NS	NS	NS	18.5	18.5	
Zhou *et al*[19] 2006	Vp234	381	NS	90	47	16	12	
Ikai *et al*[27] 2006	Vp34	78	NS	30.8	45.7	21.7	10.9	
Chen *et al*[49] 2006	Vp234	438	NS	NS	52.1	16	11.8	
	Vp23	286	13.3	60.1	58.7	22.7	18.1	
	Vp34	152	NS	62.5	39.5	5.7	0	
Nagano *et al*[17] 2007	Vp3	15	NS	66.7	100	74	NS	Postop 5-FU/IFN
	Vp3	15	NS	40	41	22	NS	
Kamiyama *et al*[12] 2007	Vp34	15	100	66.7	86.2	43.5	34.8	Preop radiation
	Vp34	28	85.7	64.3	39	13.1	13.1	
Liang *et al*[20] 2008	Vp34	33	54.5	93.9	46.8	14.4	NS	Postop PIAF
	Vp34	53	69.8	92.5	23.4	5.8	NS	
Peng *et al*[22] 2009	Vp34	51	86.3	NS	50.9	33.8	21.5	Postop TACE
	Vp34	53	86.8	NS	33.3	17	8.5	
Ban *et al*[57] 2009	Vp34	45	66.7	42.2	69.6	37.4	22.4	
Shi *et al*[48] 2010	Vp3	169	99.4	81.1	38.2	17.7	NS	
	Vp4	78	97.4	87.2	24.7	3.6	NS	
	Vp4[1]	20	95	90	18.3	0	NS	
Zhou *et al*[21] 2011	Vp34	21	NS	NS	47	22	NS	
	Vp34	38	NS	NS	70	20	NS	Adjuvant chemotherapy *via* portal vein
Matono *et al*[45] 2012	Vp34	19	NS	55.2	62.1	24.1	17.2	
	Vp34[2]	10	NS	NS	38.5	0	0	
Chen *et al*[50] 2012	Vp34	88	84.1	89.8	31.1	18.3	15.2	
Peng *et al*[46] 2012	Vp3	68	NS	NS	46.3	17.2	17.2	
	Vp4	83	NS	NS	32.5	3.6	3.6	
	Vp4[1]	23	NS	NS	21.7	0	0	
Tang *et al*[43] 2013	Vp234	186	91.9	85.5	40.1	17	13.6	
Li *et al*[58] 2013	Vp3	10	100	100	43	16	NS	
	Vp3[3]	20	100	90	32	11	NS	
Chok *et al*[47] 2014	Vp3	71	95.8	90.1	45.8	22.7	11.2	
	Vp3[4]	10	90	100	50	12.5	12.5	
	Vp34[5]	7	85.7	100	28.6	14.3	14.3	
Fukumoto *et al*[25] 2014	Vp234	41	NS	NS	80.5	32.4	NS	Postop PIHP
Yamamoto *et al*[44] 2015	Vp34	10	NS	NS	NS	NS	30	
Pesi *et al*[59] 2015	Vp3	21	NS	NS	60	39	10	
Kojima *et al*[18] 2015	Vp34	27	92.6	33.3	77.8	48.2	25.9	Postop HAIC (FP, epi-ADM)
	Vp34	25	88	32	68	32	12	
Xiao *et al*[60] 2015	Vp2	28	NS	NS	53.6	25	25	
	Vp3	38	NS	NS	39.5	15.8	5.3	
Bai *et al*[23] 2016	Vp23	51	92.2	22	19.6	NS	NS	
	Vp23	31	96.8	19	53.3	NS	NS	Postop TACE
	Vp23	10	100	30	71.1	NS	NS	Postop radiation
Zheng *et al*[51] 2016	Vp234	96	78.1	58.3	86.5	60.4	33.3	
Li *et al*[30] 2016	Vp4	39	88.9	82.2	69	NS	NS	Preop radiation
	Vp23	50	84	88	35.6	NS	NS	
Ye *et al*[24] 2016	Vp4	54	NS	85.2	0	NS	NS	Postop TACE
Hamaoka *et al*[33] 2017	Vp34	7	100	NS	100	71	NS	Preop radiation, HAIC (FP, IFN/5-FU)

[1]Tumor thrombi involving the superior mesenteric vein; [2]Non-curative resection; [3]Hepatectomy with caudate lobe; [4]PVTT extending to or beyond the portal vein bifurcation, treated by en bloc resection followed by portal vein reconstruction; [5]PVTT extending to or beyond the portal vein bifurcation, treated by thrombectomy. OS: Overall survival; HBV: Hepatitis B virus; Vp2: Tumor thrombus in the second branches of the portal vein; Vp3: Tumor thrombus in the first branch of the portal vein; Vp4: Tumor thrombus extension to the trunk or the opposite-side branch of the portal vein; TACE: Transarterial chemoembolization; PVI: Portal vein infusion; HAI: Hepatic arterial infusion; PIAF: Cisplatin, doxorubicin and 5-fluorouridine (5-FU) locally administered in the portal vein with subcutaneous injection of interferon-α; PIHP: Percutaneous isolated hepatic perfusion; FAIT: FU arterial infusion and interferon therapy; HAIC: Hepatic arterial infusion chemotherapy; FP: Cisplatin+5-FU; ADM: Adriamycin; NS: Not stated.

outcome was achieved when hepatectomy was pre- or postoperatively combined with multidisciplinary treatment. The multidisciplinary treatments included the following: Preoperative radiotherapy (RT) on PVTT in the main trunk or first branch[12]; preoperative TACE[13]; subcutaneous administration of interferon-alpha (IFN-α)

and intra-arterial infusion of 5-fluorouracil (5-FU)[17]; Epi-Adriamycin/cisplatin+5-FU[18]; cisplatin+5-FU infused in the portal vein or in the proper hepatic artery[19]; PIAF regimen (cisplatin, doxorubicin and 5-FU locally administered in the portal vein with subcutaneous injection of IFN-α)[20]; adjuvant chemotherapy (5-FU and Adriamycin) *via* the portal vein[21]; postoperative TACE[22-24]; percutaneous isolated hepatic perfusion (PIHP)[25]; and hepatic artery infusion and/or portal vein chemotherapy[26].

It was reported that the survival periods of approximately 10% of patients with tumor thrombi in the first branch and the portal trunk is more than 5 years following hepatectomy and that postoperative multidisciplinary treatments, including local and systemic adjuvant chemotherapy, are required in addition to hepatectomy to prevent intrahepatic metastasis[27]. Fukumoto *et al*[25] described that the efficacy of PIHP for hepatectomized patients with macroscopic PVTT had a median OS of 23 mo compared with a 6.5 mo median survival for patients treated with sorafenib[15]. However, PIHP treatment requires special equipment/expertise that is not currently available outside of Kobe University. On the other hand, Minagawa *et al*[13] reported the survival rate of 42% at 5 years for patients who underwent hepatectomy with preoperative TACE, which can be easily performed in any center, with only 9 cases exhibiting portal vein invasion in the second-order branches. It was reported that treating 15 cases of HCC with PVTT using FU arterial infusion and interferon therapy (FAIT) in addition to surgery, and 100% of the patients survived more than 1 year. In contrast, 10 patients (67%) died within 1 year without FAIT and surgery[17]. Peng *et al*[22] conducted a randomized controlled trial and showed that postoperative TACE enhances the effect of liver resection combined with PVTT removal. Estimated 1-, 3- and 5-years survival rates were better in the TACE group (50.9%, 33.8%, and 21.5%, respectively) than in the control group (33.3%, 17.0%, and 8.5%, respectively).

Liang *et al*[20] reported that the efficacy of intra-portal infusion chemotherapy using the PIAF regimen. They describe their procedure for administration of chemotherapeutic agents into portal vein as an attempt to kill the residual cancer cells in the portal venous system and subsequently curtail postoperative cancer recurrence. Moreover, another randomized controlled trial reported that postoperative TACE combined with portal vein chemotherapy is beneficial for patients with HCC complicated by PVTT but that the long-term efficacy of this approach is uncertain[28]. A combination of hepatectomy and preoperative RT has been reported to be effective for PVTT in the first branch or main trunk[12]. The survival rates at 1-, 3-, and 5-year were 100%, 53.3%, and 40.0%, respectively. Therefore, one of the abovementioned perioperative treatments combined with hepatectomy for HCC with PVTT might be necessary to prolong patient survival, though which of these options are superior cannot be concluded from this review. More appropriate regimens of perioperative treatment continue to be developed. Because Ando *et al*[7] reported that hepatic arterial infusion chemotherapy (HAIC) with 5-FU and low-dose cisplatin may be a beneficial therapeutic option for patients with HCC with PVTT in the main portal trunk or in the first portal branch or in the second portal branch; this regimen may be promising as adjuvant therapy for hepatectomy in HCC with macroscopic PVTT.

As a curative treatment for HCC with PVTT, only hepatectomy might be insufficient, and multidisciplinary treatments must be required because portal invasion is associated with the development of metastatic nests.

Significance of local treatment for PVTT

What about targeting PVTT for local treatment? Yamanaka *et al*[29] reported that the portal pedicles should be divided before liver parenchymal dissection during segmentectomy and lobectomy to decrease the chance of dissemination of the intravasated cancer cells because the cancer cells can dislodge into the portal venous stream during hepatectomy for HCC. From this point of view, targeting the PVTT to prevent cancer cell dissemination is a desirable approach. It was reported that preoperative radiation on the PVTT caused the tumor thrombus to become completely necrotic based on pathological examination, and 5 (83.3%) of the 6 patients survived for over 2 years after treatment[12]. Li *et al*[30] also demonstrated that better postoperative survival outcomes were provided by neoadjuvant radiotherapy before partial hepatectomy than partial hepatectomy alone for patients with HCC containing the main portal tumor thrombus. In 12 of 45 patients, the extent of PVTT after radiotherapy was significantly reduced, with the remaining 31 showing partial response (PR) and stable disease (SD) or two with progressive disease (PD)[30]. Because the tolerance of the liver for RT is low, RT for HCC has been limited to palliative treatment[31,32]. However, for the treatment of HCC, the effects of a high dose of local RT have been investigated[12,30]. Minagawa *et al*[13] described that radiation hepatitis did not occur in any of their patients and no apparent late radiation-induced complications were noted in any patients. For this reason, preoperative external RT was targeting the PVTT, not the whole tumor. By their method of RT, the irradiation in the normal liver tissue was minimized and the RT dose was increased without significantly increasing toxicity. Good survival outcome of hepatectomy with preoperative TACE for HCC patients with PVTT was reported[13]. Pathological examination detected necrosis of the PVTT in these patients. Therefore, the dissemination of HCC cells in the portal vein decrease because preoperative TACE or RT in PVTT induces necrosis. Consequently, these preoperative treatments might prevent HCC recurrence. Moreover, Hamaoka *et al*[33] reported that hepatectomy after down-staging with 3D-CRT for PVTT combined with HAIC for advanced HCC is safe and results in long-term survival outcomes. Hepatectomy for patients affected

by HCC with PVTT might prolong survival in conjunction with local treatment targeting PVTT: RT or TACE.

Operative mortality of hepatectomy for PVTT

Hepatectomy was indicated for living donor liver transplantation and the following liver tumors: Metastatic liver tumor, HCC, biliary malignancy. Of all the local treatments, hepatectomy for HCC had the highest local controllability and yielded a good survival outcome[34,35]. The liver functional reserve was decreased in almost all the patients with HCC because almost of patients with HCC had hepatitis B and/or hepatitis C viral infection and therefore had chronic hepatitis or cirrhosis[1]. Patients with liver cirrhosis decreased reticuloendothelial system functions, had elevated portal venous pressures, and impaired liver regeneration and coagulopathy[36]. Therefore, the mortality rates of hepatectomy in patients with liver cirrhosis was high form 8.9% to 19.6%[37]. On the other hand, recent advances in pre- and postoperative care, the decision criteria for hepatectomy and indications for hepatectomy and surgical techniques have been applied to extended hepatectomy[38-40]. Although operative mortality is not avoided even in donor hepatectomy for living donor liver transplantation, major hepatectomy become more safe by these preoperative evaluations[41].

There were 6 papers that reported mortality within 30 d. In Ohkubo *et al*[11]'s series, one patient died within 1 mo of the operation due to liver failure. In Capussotti *et al*[42]'s report, two patients died within 30 d due to postoperative bleeding and liver failure. In Ikai *et al*[27]'s report, patients who died within 30 d were 3, two from growth of the extrahepatic metastases and another because of pulmonary bleeding. There were 2 deaths (2.3%) recorded within 30 d after the operation due to operative mortality in Liang *et al*[20]'s paper. Two patients died within 30 d of surgery due to hepatic decompensation in Tang *et al*[43]'s study. Yamamoto *et al*[44] described one patient dying within 30 d of the operation due to acute renal failure. Thirteen papers mentioned mortality or operative mortality without reporting times. No mortality was described in six of these papers. The other 7 papers showed the number of patients or percentage of mortality. Fan *et al*[26] reported an operative mortality of 4.8%. In the control group, two patients died from operative complications in Peng *et al*[22]'s study. One patient in Matono *et al*[45]'s report died of operative morbidity. In Peng *et al*[46]'s report, there was one in-hospital postoperative death due to liver failure. The overall hospital mortality was 3.4% (n = 3) in Chock *et al*[47]'s study. There was one in-hospital death after the operation caused by postoperative bleeding (n = 169) in Shi *et al*[48]'s series. Operative mortality of Group A was 0% and that of Group B was 2.6% in Chen *et al*[49]'s paper. Chen *et al*[50] reported a mortality of 4.5%. Ye *et al*[24] reported that 5 patients died (9.3%) (liver failure: 3, serious infection: 1, and heart failure: 1). Zheng *et al*[51] reported that 1 in-hospital postoperative death (1.0%) occurred in the hepatic resection group, caused by a serious postoperative infection. Mortality on postoperative day 38 and 58 was described in studies by Capussotti *et al*[42] and Minagawa *et al*[13], respectively (Table 2).

When an HCC with major PVTT is surgically resected, a major hepatectomy should be performed with removal of the parenchyma fed by the portal vein obstructed by the PVTT vein. This operative procedure is quite technically complicated. In Asiyanbola *et al*[52]'s report, the type of operative procedure (more than or equal to hemi-hepatectomy *vs* less than hemi-hepatectomy) was related with in-hospital mortality and, specifically, patients who underwent more than or equal to a hemi-hepatectomy had a mortality rate of 6.5% compared with 4.1% for patients who underwent less than a hemi-hepatectomy. Therefore, major hepatectomy requires a very refined technique[52]. However, the operative mortality for hepatectomy in HCC with macroscopic PVTT has not been discussed. In the present review, the highest rate of operative mortality found in the literature was 9.3%[24]. The rest were not as high compared to the rates reported by Asiyanbola *et al*[52], though the mortality data were represented in a variety of ways. Major hepatectomy for HCC with macroscopic PVTT has been safely performed in many cases. The estimated cause was that the majority of patients described in this review paper had a Child-Pugh A and were infected with HBV (Table 1) and thus had a good liver function reserve. Therefore, we propose that the indication for hepatectomy in HCC with major PVTT should be expanded.

LONG-TERM SURVIVAL-RELATED FACTORS: THE EXTENT OF THE TUMOR THROMBUS

What are the long-term survival-related factors? Shi *et al*[48] previously classified PVTT into 4 groups by the extent of the tumor thrombus. Patients of types I and II: PVTT located in the segmental, sectoral, or right and/or left portal veins showed significantly better survival than those of types III and IV: PVTT extended to the main trunk of the portal vein or the superior mesenteric vein. Therefore, they concluded that hepatectomy with thrombectomy is justified in selected patients with HCC and PVTT located in the first, second, or lower branch of the portal vein. Zheng *et al*[51] also reported that the long-term survival in patients with type I and II PVTT was remarkably improved compared with in patients with type III and IV PVTT. Moreover, Kokudo *et al*[53] reported data from the nationwide survey of patients with primary liver cancer performed by the Liver Cancer Study Group of Japan, which stated that the survival benefit of liver resection was statistically significant only in patients with PVTT invading the main trunk or contralateral branch. From these data, while HCC with PVTT located in the first or second branch of the portal vein might be a relatively

Table 2 Patient mortality

	Ref.	Patient number or percent	Cause of death
Within 30 d			
	Ikai *et al*[27]	3	Pulmonary bleeding
			Extrahepatic growth
	Yamamoto *et al*[44]	1	Renal failure
	Ohkubo *et al*[11]	1	Liver failure
	Capussotti *et al*[42]	2	Postoperative bleeding
			Liver failure
	Liang *et al*[20]	2	
	Tang *et al*[43]	2	Decompensation
38 d			
	Capussotti *et al*[42]	1	Sepsis
58 d			
	Minagawa *et al*[13]	1	Liver failure
Operative mortality			
	Fan *et al*[26]	4.80%	
	Peng *et al*[22]	2	Operative complication
	Matono *et al*[45]	1	
	Peng *et al*[46]	1	Liver failure
	Chock *et al*[47]	3.40%	
	Shi *et al*[48]	1	Postoperative bleeding
	Zheng *et al*[51]	1	Serious postoperative infection
	Ye *et al*[24]	9.30%	Liver failure, serious infection, heart failure
Mortality			
	Chen *et al*[49]	0%	
		2.60%	
	Nagano *et al*[17]	0%	
	Kamiyama *et al*[12]	0%	
	Ban *et al*[57]	0%	
	Chen *et al*[50]	4.50%	
	Fukumoto *et al*[25]	0%	
	Li *et al*[30]	0%	

good indication for hepatectomy, hepatectomy for HCC combined with PVTT in the contralateral branch or main trunk should be performed after careful consideration.

Long-term survival-related factors: Liver function

Ikai *et al*[27] reported that the absence of ascites, prothrombin activity, and tumor diameter are independent prognostic factors reflecting portal hypertension, liver function and tumor status, respectively. Kondo *et al*[54] reported negative prognostic factors of hepatectomized patients with PVTT, including age < 60 years and factors related to liver function: Total serum bilirubin > 0.8 mg/dL and serum alkaline phosphatase > 300 IU/mL. Pawlik *et al*[55] concluded that patients with HCC and the major vascular invasion of the main portal or hepatic vein branches derive long-term resection benefits if they have no, or minimal, underlying fibrosis. In another report, the presence of fibrosis: Moderate to severe was the individual significant predictive factor on multivariate analysis that was related with worse short-term (≤ 6 mo) and long-term (> 6 mo) survival. In this paper, the authors argued that this result is due to postresection hepatic decompensation and to a "field cancerization"[56] effect in the cirrhotic liver, which places these patients at a higher risk for metachronous or synchronous disease. Most of the patients described in the studies we reviewed had a Child-Pugh A and were infected HBV (Table 1). This status might be a requirement for adaptation to hepatectomy to prevent postoperative hepatic decompensation. Moreover, increased liver function reserve might lead to a better prognosis for patients with HCC complicated by PVTT after hepatectomy due to the prevention of synchronous or metachronous tumors. Of the HCC patients with macroscopic PVTT, the indication of hepatectomy should be restricted within good liver function reserve.

A limitation of this review is that most of the articles selected were published from Eastern Asian countries, and the findings may not be applicable to other regions of the world. A more comprehensive review of the global literature would be very valuable in the future.

CONCLUSION

Hepatectomy might prolong the survival of patients with HCC with PVTT when the liver function reserve is preserved, such as in Child-Pugh score A cases. Effective multidisciplinary treatments may improve the prognosis and prevent recurrence due to disseminated cancer cells in these patients. Moreover, hepatectomy may be a feasible adjunct treatment for HCC with PVTT due to the current mortality rates after hepatectomy being quite low.

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MINIREVIEWS

Molecular basis of hepatocellular carcinoma induced by hepatitis C virus infection

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Abstract

Present study outlines a comprehensive view of published information about the underlying mechanisms operational for progression of chronic hepatitis C virus (HCV) infection to development of hepatocellular carcinoma (HCC). These reports are based on the results of animal experiments and human based studies. Although, the exact delineated mechanism is not yet established, there are evidences available to emphasize the involvement of HCV induced chronic inflammation, oxidative stress, insulin resistance, endoplasmic reticulum stress, hepato steatosis and liver fibrosis in the progression of HCV chronic disease to HCC. Persistent infection with replicating HCV not only initiates several liver alterations but also creates an environment for development of liver cancer. Various studies have reported that HCV acts both directly as well as indirectly in promoting this process. Whereas HCV related proteins, like HCV core, E1, E2, NS3 and NS5A, modulate signal pathways dysregulating cell cycle and cell metabolism, the chronic infection produces similar changes in an indirect way. HCV is an RNA virus and does not integrate with host genome and therefore, HCV induced hepatocarcinogenesis pursues a totally different mechanism causing imbalance between suppressors and proto-oncogenes and genomic integrity. However, the exact mechanism of HCC inducement still needs a full understanding of various steps involved in this process.

Key words: Hepatitis C virus; Hepatocellular carcinoma; Fibrosis; Core; NS5A; Inflammation

Core tip: Hepatocellular carcinoma (HCC) is one of the most common cancer occurring in human population all over the world. Chronic hepatitis C virus (HCV) infection is considered as a major cause of producing

HCC in developed countries. HCV infection induces chronic inflammation in liver, which initiates several changes including production of oxidative stress, steatosis, progressive fibrosis, cirrhosis and finally HCC. HCV related proteins also interact directly with cellular proteins at various steps of cell signaling disturbing cell cycle and regeneration process. HCC is supposed, now a days, to be the foremost indication for liver transplant.

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INTRODUCTION

Hepatitis C virus (HCV) infection is a global health problem reported from all parts of the world. HCV was characterised by Choo *et al*[1] and Kuo *et al*[2] in 1989. As per World Health Organization report, about 3% world population is having HCV infection with 170 million people becoming as chronic carriers of HCV[3]. These people always remain at high risk of developing cirrhosis of liver and hepatocellular carcinoma (HCC) in later years. There is an increase in the cases of HCC with 1%-7% chronic HCV infected patients developing HCC after establishment of cirrhosis[4,5]. HCC caused by HCV infection is a prominent indication for liver transplant[6].

HCV is an enveloped RNA virus included under Flaviviridae family[7]. It has 9.6 kb single stranded RNA with positive polarity. HCV genome encodes a long protein of 3000 amino acids which undergoes proteolysis to yield structural proteins (Envelop E1, E2 and Core) and nonstructural proteins (P7, NS2, NS3, NS4A, NS4B, NS5A and NS5B)[8]. Whereas structural proteins play important role in its morphological features and entry into the host cell, nonstructural proteins are involved mainly in viral replication, assembly and pathogenesis of diseases caused. HCV genome is highly heterogeneous with 32%-35% variations in different HCV genotypes[9]. Based on current reports at least seven genotypes and several subtypes of HCV have been reported till date[10]. Although, variability of genomic sequence has been reported throughout the viral genome, the E1 and E2 regions have been reported to be maximally variable[10].

HCC develops more frequently in cirrhotic patients in comparison to those having mild fibrosis[11]. In addition, hepatitis B virus infection, insulin resistance, obesity and steatohepatitis also promote HCV related HCC[12]. HCC may result from a combined effect of host, environment and viral factors[13]. Immune mediated chronic inflammation during HCV infection is supposed to facilitate the development of HCC. Simultaneously, it may induce HCC by altering many cell pathways involved in cell proliferation, energy metabolism, and apoptosis[14].

As such, HCV is a non-cytopathic virus and initiates hepatic injury by immune mediated reaction-cascade. Although, it is not fully established, however, on the basis of animal experiments and human studies, it is assumed that HCV plays both direct as well as indirect role in inducing HCC[15,16]. Current literature demonstrates that cell death, regeneration, inflammation, oxidative stress and steatosis noted during chronic HCV infection are some of the main reasons responsible for hepatocarcinogenesis[13,17]. Similarly, dysregulation of cell cycle by altered intracellular signaling cascade arising during chronic HCV infection is an important phenomenon in the direction of HCC development. In fact, mechanism of hepatocarcinogenesis during chronic HCV infection is slightly distinct from those responsible for causing other types of cancers. HCV core protein was found to induce HCC in absence of genetic aberrations and so, this was named as "non- Vogelstein- type" carcinogenesis in some reports[18]. This may explain a high incidence and multicentric nature of HCC developed during HCV infection. Present review describes a compilation of informations on the mechanisms of HCC development during chronic hepatitis C virus (HCV) infection.

MECHANISMS OF HCV INDUCED HCC

HCV is a hepatotropic virus and enters host cell *via* a complex sets of molecules present on cell surface including CD81 (receptor molecule), SRB-1 (scavenger receptor) and Occludin-1 and Claudin (tight junction proteins)[19-21]. After its entry, HCV replicates in hepatocytes and leads to different types of cellular and immune mediated changes. A majority of patients infected with HCV fail to clear the virus. In these patients HCV persists for longer duration causing chronic HCV infection and a high risk for progressive hepatic fibrosis, cirrhosis and HCC[22]. Simultaneously, the ensuing chronic inflammation associated with oxidative stress and emerging cellular DNA damage, also contribute to development of HCV associated HCC. The question whether cancer develops in infected hepatocytes or in uninfected hepatocytes still needs to be answered. Based on some experimental studies it was reported that Ki67 proliferation marker is raised in advanced HCV infected hepatocytes pointing towards HCV infected cells at higher risk for HCC as compared to uninfected cells[23,24]. Several studies suggest that liver cancer develops by an interplay of host, viral and environmental factors. All these finally bring some epigenetic changes in HCV infected hepatocytes leading to development of HCC[13,25].

Chronic HCV infection is often accompanied by several disturbances including inflammation, steatosis and progressive fibrosis in the liver[25]. All these changes ultimately progress to cirrhosis and hepatocarcinogenesis. Therefore, it is suggested that HCC is caused by an interplay of chronic inflammation, insulin resistance

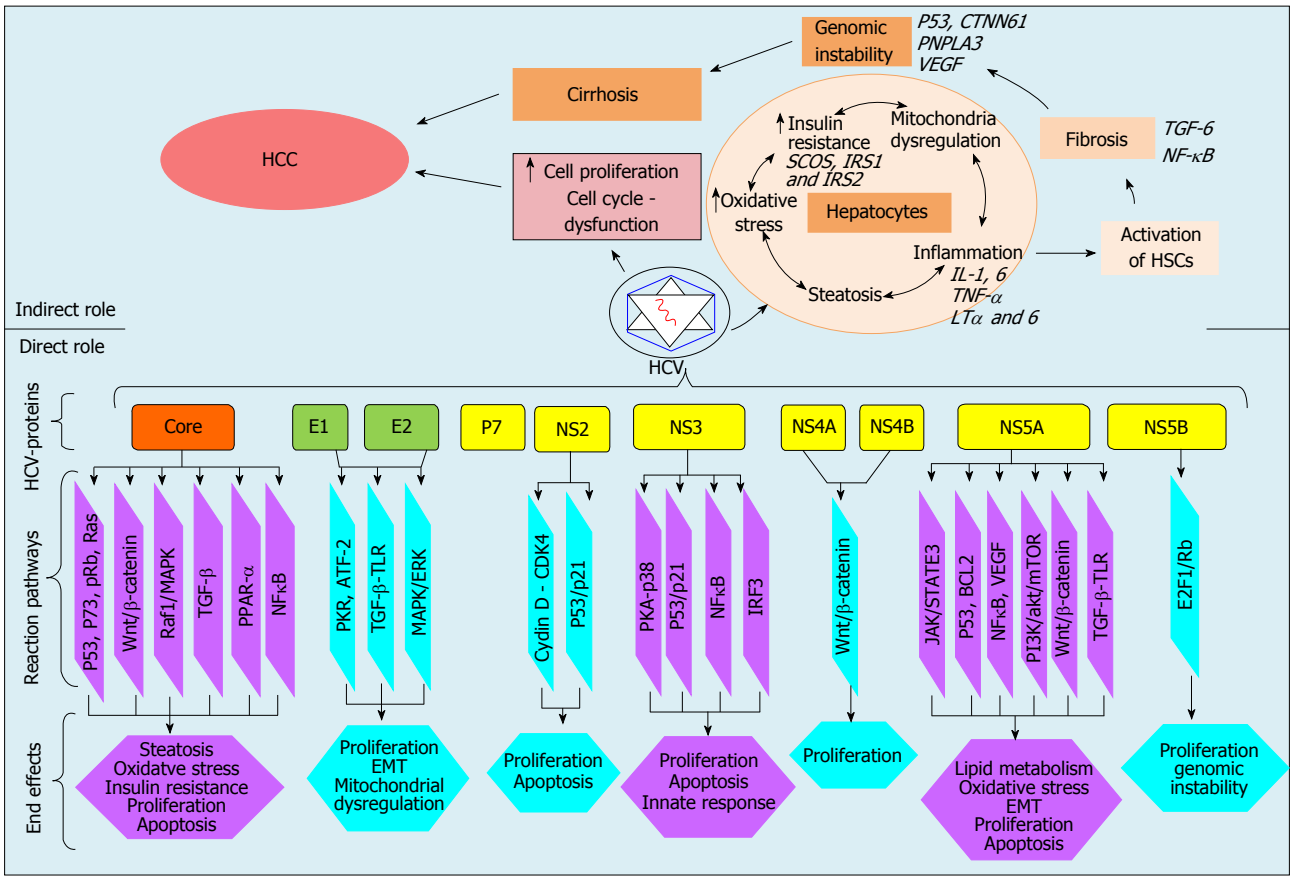

Figure 1 Direct and indirect role of hepatitis C virus in causing hepatocellular carcinoma. Role of hepatitis C virus (HCV) and its structural and non-structural proteins in inducement of hepatocellular carcinoma (HCC) during chronic HCV infection. Viral onset causes various cellular alterations leading to activation of hepatic stellate cells which in turn, produce progressive fibrosis leading to cirrhosis of liver. Simultaneously, HCV also dysregulates cell cycle causing cell proliferation. Both cirrhosis and cell proliferation induce development of HCC. In this figure, the top half portion shows an indirect role of HCV *via* cellular alterations and causing cirrhosis by inter-related mechanisms and cell dysregulation leading to cell proliferation. The lower half shows a direct role of HCV by interaction of its proteins with various cellular pathways producing different effects as preconditions for inducement of HCC. The link bars show the underlying pathways and the bottom boxes show the end effects. EMT: Epithelial to mesenchymal trans-differentiation; HSCs: Hepatic stellate cells; TGF: Transforming growth factor; PKR: Protein kinase; VEGF: Vascular endothelial growth factor; TNF-α: Tumor necrosis factor-α; PPAR-α: Peroxisome proliferator-activated receptor alpha; ERK: Extracellular signal regulated protein kinase; PKA: Protein kinase A; NF-κB: Nuclear factor-κB.

(IR), hepatosteotasis, oxidative stress, fibrosis, and the resulting liver damages by chronic HCV infection. This interplay produces a pro-oncogenic microenvironment which promotes fibrogenesis and genetic instability[26]. Simultaneous with a direct transforming role of HCV, the liver microenvironment is supposed to have a modulating effect on cell transforming process during HCC development. Several HCV proteins have direct oncogenic effects and use liver changes in upregulating mitogenic process[27]. At the same time, increasing cell proliferation in this environment also results in DNA damage causing genomic disturbances. This becomes another basis for malignant transformation of hepatocytes. In view of all these available reports[25-27], the mechanism of HCV induced HCC may be illustrated by a direct and indirect role of HCV in relation to the microenvironment produced by chronic HCV infection (Figure 1).

HOST FACTORS

Inflammation and oxidative stress in HCV induced HCC

Immune mediated inflammation caused during chronic HCV infection indirectly triggers hepatocarcinogenesis. Simultaneous with a direct role of HCV in inducement of HCC by altering several cellular pathways involved in metabolism, DNA repair and apoptosis[14], chronic HCV infection enhances the reactive oxygen species (ROS) which damages the liver cells. At the same time, HCV also induces inflammation by activating hepatic stellate cells (HSCs)[28]. These HSCs get activated by ROS, growth factors, cytokines, adipokines and chemokines secreted by hepatocytes, Kuffer cells and inflammatory cells[29]. The progress of disease is increased by cumulative effect of inflammation, ROS, steatosis and IR caused during chronic HCV infection. The activated HSCs, under the effect of fibrogenic cytokines undergo epithelial to mesenchymal trans-differentiation (EMT) into myofibroblast like cells which cause liver fibrosis[14]. Transforming growth factor beta (TGF-β) cytokine regulates EMT demonstrating its pro-oncogenic functions[30]. Hepatic fibrosis is closely associated with HCC development. EMT pathway plays a major role in transition of hepatocyte to cancerous cell and process of metastasis known with expression of E-cadherin and

Vimentin[31]. The IR stimulates HSCs and links fibrosis with steatosis. The process of fibrogenesis is regulated by a number of signaling pathways including SMADs, phosphatidylinositide 3-kinases (PI3K), protein kinase (Akt), mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinases (JNKs) pathways. JNK activation by IL1-β cytokine increases fibrogenesis, oncogenesis and cell motility[32,33]. Thus all these liver alterations finally produce a suitable environment for development of HCC in chronic HCV infection.

Insulin resistance and hepato steatosis in HCV induced HCC

It has been observed that HCV *genotype-3* induces steatosis in patients with chronic HCV infection[34]. HCV induces steatosis by increasing lipid synthesis and reducing its secretion and degradation. The structural and nonstructural proteins of HCV directly interfere in lipid synthesis[35] and very-low-density lipoprotein secretion[36,37]. These HCV related proteins also inhibit fatty acid oxidation[38,39] and enhance fatty acid release from adipocytes[34]. All this finally results in hepatic steatosis. The HCV related proteins are also involved in producing ROS[40] and glucose homeostasis. HCV interferes with insulin signaling by proteosomal degradation of insulin receptor substrate 1 (IRS-1) and IRS-2 by suppressor of cytokine signaling (SOCS) protein or PI3K/Akt/mTOR pathway. IRS-1 is reported to be inactivated by TGF-α and PI3K/Akt also[41]. In this manner, the early stage of chronic HCV infection with increasing steatosis and IR creates an environment to help in hepatocarcinogenesis leading to development of HCC.

Immune mediated liver alteration in HCV induced HCC

HCV influences both innate and adaptive immunity. This virus inhibits type 1 Interferon production and $CD4^+$ T-cell transformation to Th2, Th17 and regulatory T-cell. This disturbs the function of cytotoxic $CD8^+$ T-cells and natural killer (NK) cells[42-48]. It results in chronic liver inflammation which disturbs tissue homeostasis and promotes pro-carcinogenic environment. Simultaneously, there is an increase in the release of ROS, nitric oxide (NO), cytotoxic cytokines and lipid peroxidation. It also helps in immune escape of neoplastic transformed cells facilitating the development of HCC[49]. During chronic HCV infection, the inflammatory cytokine like tumor necrosis factor-α (TNF-α), interleukin (IL)-1, IL-23, IL-6 and lymphotoxins-alpha and beta (LT-α and β) are also increased causing chronic liver inflammation and HCC progression[49-51]. There is already a report demonstrating an important role of LT-α and LT-β in the development of HCC[51]. In fact, activation of NF-κB pathway by LTs triggers the hepatocarcinogenesis by increasing production of chemokines and cytokines. In patients with chronic HCV infection, the liver infiltrating T and B-cells not only fail viral clearances but also increase chronic inflammation[51,52]. Also, an increased number of $CD8^+$ is accompanied by reduction in NK and NKT cells which are involved in cancer immune surveillance[52]. These informations indicate that during chronic HCV infection there is a regular tumor promoting inflammation and impaired anticancer immune scanning, which ultimately facilitates towards HCC.

Hepatic fibrosis in HCV induced HCC

As described earlier there is high occurrence of steato-hepatitis in patients with chronic HCV infection. The accumulation of free fatty acid induces production of ROS and mitochondrial dysfunction and Endoplasmic reticulum (ER) stress. In turn, oxidative stress stimulates lipid peroxidation and increases inflammation in liver tissue. Increased ROS levels have direct effect on fibrosis by increasing collagen 1 expression[50]. The HCV induced steatosis changes the liver T-cell function. HCV related proteins in the liver develop extensive steatosis which is accompanied by an infiltrate of $CD8^+$ T-cell secreting Th2 type cytokine[53]. A massive liver infiltration by $CD8^+$ and NKT cells induces steatosis, inflammation and carcinogenesis[54]. In HCV infected patients, the risk of HCC development may also be linked with the severity of liver fibrosis. TGF-β is an important cytokine involved in fibrogenesis. Its expression is directly affected by HCV related proteins or oxidative/ER stress and NF-κB pathway activation[55-58]. This concludes that hepatic fibrosis caused by various mechanisms is a big inducer promoting hepatocarcinogenesis.

Genetic factors in HCV induced HCC

There are a number of genes associated with HCV induced HCC. The tumor suppressor gene *P53* was the first one noted for its association with development of HCC. Recent studies have shown a subset of genes frequently mutated in HCV patients[59,60]. Oncogene CTNNB1 which encodes β-catenin protein of WNT-pathway shows a mutation of 30%. WNT ligands activate signal transduction cascade resulting in inhibition of β-catenin degradation complex. It has been observed that WNT pathway gets mutated in HCC, which stabilizes β-catenin. This β-catenin translocates to the nucleus and regulates genes responsible for cell survival and proliferation. NS5A indirectly regulates the WNT pathway through PI3K and activate Akt. Increased β-catenin has been observed in HCV infected cells. The significance of β-catenin with in HCV infected cells is still uncertain[61]. However, its level is increased mostly in HCC patients. Similarly, reduction in the size of telomere triggers cellular senescence. Activation mutation in the telomerase reverse transcriptase (TERT) promoter gene has been detected in HCC induced by HCV infection in addition to other etiologies[62-64]. HCV core protein downregulates CDKN2A expression to overcome hepatocyte senescence. Increased telomerase activity, a characteristic of transforming or transformation prone cells, was observed in HCV core- transfected primary human hepatocytes that acquired an immortalized phenotype. In line with this observation, somatic mutation in the

TERT promoter that enhance TERT expression were shown to be among the earliest and most prevalent neoplastic events associated with all major etiologies including HCV. Host genetic variants are also associated with a high risk of HCC[65]. *PNPLA3* gene (patatin-like phospholipase domain-containing protein-2) shows a significant association with fatty liver disease in HCV patients having a higher risk of HCC[66-68]. On a similar pattern, polymorphisms in several other cytokines/receptors genes have been found to be associated with HCC. These are cytokines *TNF-α*, *IL-10*, *IL-23R* and vascular endothelial growth factor (*VEGF*) *etc.* genes. Host responds differently to variation in viral genome. For example, HCV genotype 1a and 1b reported to be associated with HCC[69].

Epigenetic alterations in HCV induced HCC

Various studies have demonstrated a dysregulation of epigenetic regulatory genes in HCC[70]. Histone-lysine N-Methyltransferase enzyme (EZH2) is one such an example which is aberrantly expressed in HCC[71] and this also targets expression of tumor suppressor miRNAs[72]. The changes in gene methylation were also related with virus induced tumors[73]. Various tumor suppressor genes including CDKN2A, GSTP1, RUNX3, APC, SOCS-1 and RASSF1A are highly methylated in HCC caused by HBV and HCV infection[74]. Epigenetic alterations in HCC may be mediated by changes in miRNAs and long noncoding RNAs. There are several miRNAs which modulate HCV replication in a positive and negative manner[75].

Neoangiogenesis in HCV induced HCC

Structural and nonstructural HCV proteins have a direct role in inducing neoangiogenesis. HCV core promotes angiogenesis by upregulating hypoxia inducible factor 1-alpha which regulates VEGF and cyclooxygenase 2. VEGF is an important endothelium specific growth factor in HCC and for this reason, VEGF level in serum is used as a prognostic factor in HCC[76]. Angiopoietin-2 is also upregulated by HCV infection[77].

VIRAL FACTORS

HCV replicates and releases its protein component in cytosol. HCV related proteins which have a major role in regulating viral replication and HCV particle assembly, have been demonstrated to influence several cell signal pathways and metabolic mechanisms indicating their role in cell cycle and cell transformation. Both structural and nonstructural proteins interact with different host cellular proteins to promote malignant transformation of hepatocytes. Based on these studies we describe here the role of each individual HCV protein in the process of cell transformation to malignant liver cell.

Core protein

HCV core protein, which regulates HCV RNA translation and its replication, interacts with component proteins of various cell-signaling pathways. In addition, this protein modulates host immune response, oxidative stress, lipid metabolism and also apoptosis[78]. In some recent studies on HCV infected patients, core gene has been found to undergo frequent mutations[79]. The role of core protein in the development of HCC was studied in transgenic mouse model. The information collected from these studies indicate that core gene overexpression results in steatosis in early life with development of adenoma and HCC in later years[80]. In few other studies, the presence of steatosis in liver induced by core protein could not be related to HCC development[29,81]. According to recent reports, core protein shows interference with cellular proteins and it is considered as a major risk factor for the progression of HCC[82]. Of course, the presence of core protein has been associated with its activation of lipogenic pathway in HCC cases[83]. Core protein often remains associated with lipid droplets in CHC cases and possibly causes steatosis through several mechanisms including peroxisome proliferator-activated receptor alpha and sterol-regulatory element binding protein-1 pathways[46,81,84].

Similarly, core protein also interacts with ER or mitochondria and induces ER stress by accumulation of ROS[85]. ROS causes DNA damage and accelerates hepatocarcinogenesis. The effect of HCV core have also been demonstrated on signaling pathways responsible for cell cycle like stimulation of G_1/S transition by increasing the levels of cyclin E/Cdk2[86] and apoptosis. Core protein interacts with tumor suppressor including P53, P73 and P21[87] as well as regulator of apoptosis like TNF-α signaling or Bcl-2 members. Core proteins also effects growth and proliferation of cells through activation of signaling pathways like RAF/MAPK (Mitogen activated protein kinase)[88], Wnt/β-catenin and TGF-β[39,89]. All these pathways have been reported to be active in HCC. Therefore, these findings about HCV core indicate that this protein has a potential role in cell proliferation and reduction of apoptosis during development of HCC.

E1/E2 protein

The effect of structural proteins E1/E2 was also studied on malignant transformation of hepatocytes. The results indicated these proteins to interfere with Interferon actions by inhibiting dsRNA protein kinase (PKR)[90,91]. In addition, E2 protein also inhibits activation of T and NK cells[91] and MAPK/extracellular signal regulated protein kinase pathway including the transcription factor ATF-2 and promotes cell proliferation and cell survival[92].

NS2 protein

NS2 activates cyclin D/CDK4 and induces expression of Cyclin E[93]. Some studies also supported its role in the inhibition of apoptosis by interference with p53 pathway.

NS3 protein

The NS3 transforms mammalian cells but its role in

HCC is less clear[94,95]. This protein interacts with tumor suppressor p53. NS3 protein modulates various signal transduction pathways having transformation potential. NS3 interacts with protein kinase A and inhibits its translocation to nucleus. NS3 also inhibits interferon response factor (IRF-3) mediated induction of type-1 interferon, necessary to escape immune surveillance. NS3/4A interacts with ATM, Check point kinase, preventing DNA repair. This also disturbs endoplasmic reticulum leading to cell death[96]. Similarly, NS3/4A target adaptor molecules in TLR3 and RIG-1 signal pathway, thereby interfering with activation of IRF-3 transcription factor and promoting proliferation[97-99]. All these reactions contribute to cancer promoting effect of HCV.

NS5A protein

This protein is needed for replication of HCV genome. It forms part of viral replicates complex. Inside the nucleus, NS5A acts as transcription factor activator[100] and interacts with various signaling pathways including cell cycle/apoptosis, lipid metabolism[46,101] and also shares some signaling targets with core. It has been reported to interfere with PKR-p38 signaling pathway and inducing aberrant mitosis and chromosomal instability leading to HCC[102]. NS5A inhibits TGF-β signaling by preventing nuclear translocation of SMAD proteins down regulating tumor suppressor CDKN1A[103]. On a similar pattern, NS5A inhibits tumor necrosis factor-α (TNF-α) mediated apoptosis[104]. NS5A acts a transcriptional activator for many genes including p53. NS5A also interacts with pathways like Bcl-2, PI3K, Wnt/β-catenin signal and mTOR for proliferation of cells and inhibition of apoptosis. It has been found that HCV NS5A influences EMT pathway and helps in transition process of epithelial cells to mesenchymal stem cells. NS5A work in cooperation to TGF-β to activate stellate cell causing fibrosis. Also HCV core protein was found to induce EMT in primary hepatocyte by suppressing cytostatic effect *via* SMAD3[105,106]. Thus NS5A and core produce cells in tumor mass that are not differentiated and mobile *via* EMT pathway EMT contributes to liver fibrosis on the line as in lungs, kidney and intestine.

NS5B protein

NS5B binds with Rb and promotes its cytoplasmic relocalization and proteasomal degradation[107,108]. This finally activates E2F responsive genes, which in turn stimulates cell cycle progression[108].

Above reports demonstrate a clear effect of HCV-related proteins on various pathways engaged in progression of infected cells to malignant cells. These proteins enhance the level of underlying inflammation, oxidative stress, ER stress, steatosis, fibrogenesis and finally cell proliferation. Although it is not possible to emphasis their direct effect in exclusion either on initiation or progression, but there is no doubt that involvement of these proteins at various steps of complex mechanism, helps in progression of carcinogenesis resulting in development of HCC.

CONCLUSION

This update on the development of HCC following chronic HCV infection demonstrates that HCV infection is a serious health problem recorded globally. A majority of patients progress to end stage liver diseases including liver cirrhosis and HCC. Once established, the chronic HCV infection produces several changes in the liver including chronic inflammation, insulin resistance, oxidative stress, steatosis and continuing liver fibrosis. These changes are caused by the mechanism influenced either directly or indirectly by HCV particles. HCV related proteins interact with several cellular proteins thereby modulating cell signaling. Similarly, chronic inflammation caused by HCV inflammation also promotes all above liver changes. During this interplay of various reaction cascade there is possibility of genomic imbalance disturbing the normal reactions leading to abnormal cell cycle and apoptosis. The cumulative effect of all these finally facilitates the tumorigenesis in liver causing HCC. Although several lines of information are available, however, much more still needs to be answered to extricate this mystery.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Recent trends in liver transplantation for alcoholic liver disease in the United States

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Abstract

AIM

To examine temporal changes in the indications for liver transplantation (LT) and characteristics of patients transplanted for alcoholic liver disease (ALD).

METHODS

We performed a retrospective cohort analysis of trends in the indication for LT using the United Network for Organ Sharing (UNOS) database between 2002 and 2015. Patients were grouped by etiology of the liver disease and characteristics were compared using χ^2 and *t*-tests. Time series analysis was used identifying any year with a significant change in the number of transplants per year for ALD, and before and after eras were modeled using a general linear model. Subgroup analysis of recipients with ALD was performed by age group, gender, UNOS region and etiology (alcoholic cirrhosis, alcoholic hepatitis and hepatitis C - alcoholic cirrhosis dual listing).

RESULTS

Of 74216 liver transplant recipients, ALD (n = 9400, 12.7%) was the third leading indication for transplant after hepatitis C and hepatocellular carcinoma. Transplants for ALD, increased from 12.8% (553) in 2002 to 16.5% (1020) in 2015. Time series analysis indicated a significant increase in the number of transplants per year for ALD in 2013 (P = 0.03). There were a stable number of transplants per year between 2002 and 2012 (linear coefficient 3, 95%CI: -4.6, 11.2) an increase of 177 per year between 2013 and 2015 (95%CI: 119, 234). This increase was significant for all age groups except those 71-83 years old, was observed for both genders, and was incompletely explained by a decrease in transplants for hepatitis C and ALD dual listing. All UNOS regions except region 9 saw an increase in the mean number of transplants per year when comparing eras, and this increase was significant in regions 2, 3, 4, 5, 6, 8, 10 and 11.

CONCLUSION

There has been a dramatic increase in the number of transplants for ALD starting in 2013.

Key words: Alcoholic liver disease; Liver transplantation; Cirrhosis; Epidemiology; Hepatitis C

Core tip: Although the number of liver transplants done for alcoholic liver disease (ALD) has been stable been 2002 and 2012, since 2013 there has been a significant increase. This increase is seen across all age groups, although the proportional increases are higher for younger patients than older ones. The increase corresponds, but is incompletely explained, by a decrease in transplants for hepatitis C - ALD dual listing. The increase was also seen in most, but not all UNOS regions.

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INTRODUCTION

Liver transplantation (LT) has become a life-saving procedure for patients with irreversible liver diseases. A total of 7841 liver transplants were performed in 2016 in the United States with 14389 potential recipients on the waiting list[1]. One of the common causes of chronic liver disease for which LT is potentially life saving is alcoholic liver disease (ALD). Progression of ALD is dependent on patient characteristics (sex, race, ethnicity, malnutrition), genetic factors, coexisting liver pathology [*e.g.,* hepatitis C virus (HCV) or non-alcoholic steatohepatitis (NASH)] as well as drinking patterns (volume consumed, drinking outside meal times, binge drinking, and duration of consumption). The risk of developing cirrhosis is increased with consumption of > 60-80 g/d of alcohol for ⩾ 10 years for men and > 20-40 g/d in women[2,3]. However, despite drinking at these levels, only 6%-41% of people develop cirrhosis[2,4].

Population-based studies have shown that although the proportion of the population who drink any alcohol is not increasing, there has been an increase in the prevalence of both heavy drinking (defined as more than 1 drink per day for women or 2 drinks per day for men, on average) and binge drinking (defined as at least 4 drinks for women or 5 for men in the last thirty days)[5]. Heavy drinking has been shown to increase the risk of ALD and all-cause mortality[6]. Because we have noticed a recent increase in the number of referrals to our transplant center for ALD, we decided to critically review the temporal and geographic trends in the LT for ALD and examine characteristics of patients transplanted for ALD.

MATERIALS AND METHODS

Data source

We conducted a retrospective cohort analysis of transplant recipients in the United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research file. United States donor data for this analysis is Organ Procurement and Transplantation Network data released 2016-06-17 based on data collected through 2016-03-31. UNOS as the contractor for the Organ Procurement and Transplantation Network supplied this data. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the Organ Procurement and Transplantation Network or the United States Government. The statistical methods of this study were reviewed by Dr. James Perkins from the University of Washington. This study met expedited review criteria as approved by the University of Washington Institutional Review Board.

Study population and temporal trends

We identified all liver transplant recipients in the UNOS database from 2002 to 2015 and characterized them according to the etiology of their liver disease. The category ALD was defined as recipients with a diagnosis of alcoholic cirrhosis or acute alcoholic hepatitis. However, in order to minimize the effect of concomitant liver disease, we categorized those with a listing diagnosis of both HCV and alcoholic cirrhosis (HCV/ALD) as HCV.

Recipient characteristics were compared among the leading four etiologies of cirrhosis using χ^2 test for categorical values and student's t-test used for continuous variables. The number of transplants per year by liver disease was graphed to illustrate changes

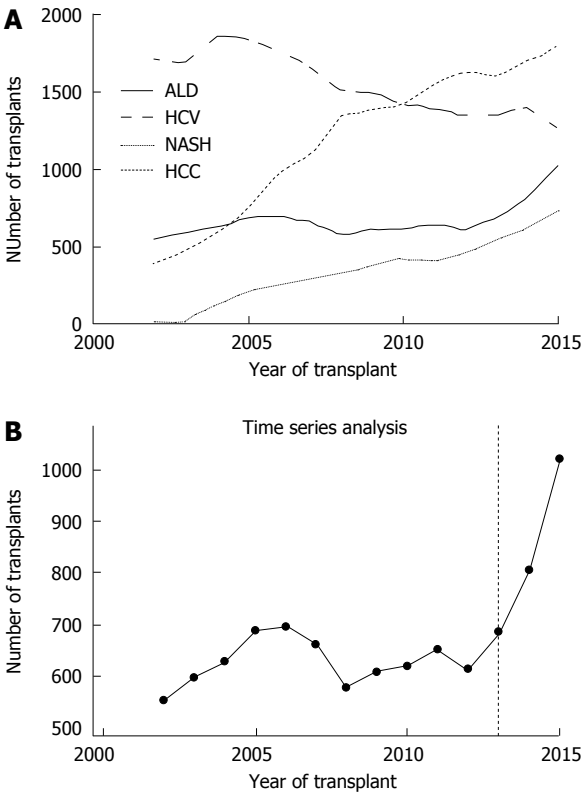

Figure 1 Time series analysis demonstrated a significant increase in the number of transplants for alcoholic liver disease starting in 2013. A: Number of transplants per year by etiology of liver disease; B: Time series analysis of alcoholic liver disease liver transplant recipients demonstrating a significant change in the number of transplants starting in 2013 (P = 0.03). ALD: Alcoholic liver disease; HCV: Hepatitis C virus; NASH: Non-alcoholic steatohepatitis; HCC: Hepatocellular carcinoma.

over time.

ALD subgroup analysis

We performed a subgroup analysis of recipients transplanted for ALD. Temporal trends in recipient characteristics were studied and compared using χ^2 test for categorical values and student's t-test used for continuous variables. We then used time series analysis to identify any year with a significant change in the number of transplants per year, and then compared transplant rates in the "before" and "after" eras. To model transplant growth in each era, we used a spline linear regression model with the cut point at the year predicted by the time series analysis.

To determine if age or gender had any affect on change in transplant rates, we also compared mean transplants per year in the before and after eras for categorical age groups (18-30, 31-40, 41-50, 51-60, 61-70 and 71-83 years old) and gender using student's t-test. We also used this method to evaluate the contribution of transplants for acute alcoholic hepatitis, separating the ALD population into acute alcoholic hepatitis from alcoholic cirrhosis subgroups. We hypothesized that the increasing use of curative treatment for HCV cirrhosis could lead to a change in the classification of cirrhosis etiology, such that patients previously listed as HCV/ALD were subsequently listed as alcoholic cirrhosis alone. Hence, we analyzed the change in time for the HCV/ALD population using the same approach as above.

Analysis of transplant changes by region

UNOS is an organization involved in many aspects of the organ transplant and donation process and operates by grouping states into several different regions throughout the country. To facilitate transplantation, the US is divided into 11 geographic regions. Liver transplant recipients were grouped by UNOS region and the mean number of transplants per region per year for the before and after eras was calculated.

Statistical analysis

Analyses were conducted using JMP Pro 13.0.0 (SAS Institute Inc. Cary, NC) statistical software, graphics were made in Stata 12.1 (College Station, TX, United States).

RESULTS

Study population

Of 74216 liver transplant recipients, ALD (n = 9400, 12.7%) was the third leading indication for transplant after HCV (n = 21707, 29.2%) and hepatocellular carcinoma (HCC) (n = 16627, 22.4%) (Figure 1A). Recipients with ALD were younger, more likely to be non-black and have a higher model for end-stage liver disease (MELD) at transplant than recipients with HCV, HCC or NASH cirrhosis (Table 1). Time series analysis demonstrated a significant increase in the number of transplants for ALD starting in 2013 (P = 0.03) (Figure 1B).

ALD subgroup analysis

The total number of transplants performed for ALD increased from 553 (12.8% of the annual total) in 2002 to 1020 (16.5%) in 2015 (Table 2). Age and BMI remained unchanged over the study period, but there was a significant increase in the proportion of female recipients (from 22.4% in 2002 to 27.5% in 2015, P = 0.001) and an increase in MELD (20.6 ± 8.4 in 2002 to 28.9 ± 10.4 in 2015, P < 0.001). In the before era, the number of transplants per year was stable as predicted by the linear spline model (coefficient 3.3, 95%CI: -4.6, 11.2). In the after era, there were approximately 177 more transplants per year for ALD (coefficient 176.7, 95%CI: 119.4, 234.0) (Figure 2).

All age groups except those 71-83 years old showed a significant increase in the mean number of transplants per year for ALD when comparing before and after eras, but the greatest proportional increase was seen in the youngest recipients (Table 3). The proportional increase in mean transplants per year was greater in females than males, and was significant for both genders (P

Table 1 Recipient characteristics by etiology of liver disease

	HCV 21707 (29.2%)	HCC 16627 (22.4%)	ALD 9400 (12.7%)	NASH 4745 (6.4%)	*P* value
Age	54.1 ± 7.19	57.9 ± 7.8	53.5 ± 9.02	56.7 ± 10.2	< 0.001
Female	5799 (26.7%)	3928 (23.6%)	2210 (23.5%)	2237 (47.1%)	< 0.001
Race					< 0.001
White	15408 (71.0%)	11133 (67.0%)	7533 (80.1%)	4006 (84.4%)	
Hispanic	3071 (14.2%)	2496 (15.0%)	1285 (13.7%)	524 (11%)	
Black	2504 (11.5%)	1542 (9.3%)	371 (4.0%)	95 (2%)	
Other	724 (3.3%)	1456 (8.8%)	211 (2.2%)	120 (2.5%)	
BMI	28.4 ± 5.3	28.3 ± 5.3	27.9 ± 5.41	32 ± 6.1	< 0.001
Diabetes					< 0.001
None	16912 (77.9%)	11741 (70.6%)	7440 (79.2%)	2139 (45.1%)	
Any	4430 (20.4%)	4733 (28.5%)	1828 (19.5%)	2545 (53.6%)	
Unknown	365 (1.7%)	153 (0.9%)	132 (1.4%)	61 (1.3%)	
MELD at transplant	22 ± 10	15 ± 8.3	25.1 ± 9.6	23.8 ± 9.2	< 0.001
HCC in explant	3919 (18.1%)	11034 (66.4%)	482 (5.1%)	260 (5.5%)	< 0.001

HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma; ALD: Alcoholic liver disease; NASH: Non-alcoholic steatohepatitis; BMI: Body mass index.

= 0.001, 0.005, respectively). Although there was a 1.4 fold increase in transplants for alcoholic hepatitis, this was not statistically significant (P = 0.58), only represented an increase of approximately 3 transplants per year, and did not explain the overall increase in transplants for ALD. As expected, there was a decrease in transplants for HCV/ALD, however this decrease (90.7 transplants per year) was much less than the per year increase for ALD (210.3 transplants per year).

Analysis of transplant and alcohol use by region

All regions except region 9 saw an increase in the mean number of transplants per year when comparing eras, and this increase was significant in regions 2, 3, 4, 5, 6, 8, 10 and 11 (Table 4, Figure 3).

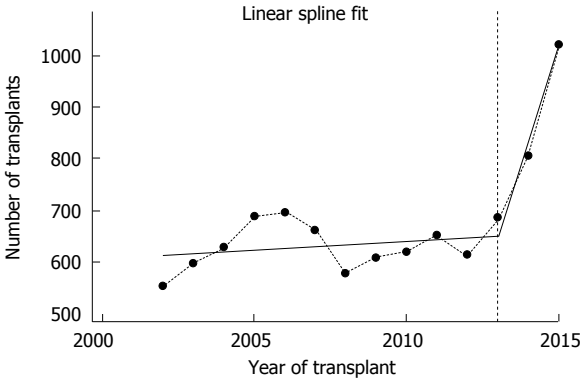

Figure 2 Linear spline fit for number of transplants for year for alcoholic liver disease in the before and after eras.

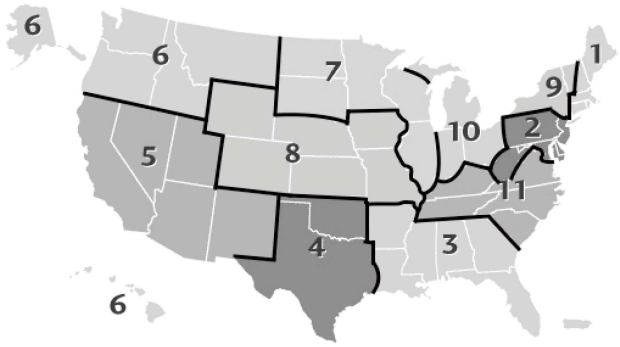

Figure 3 UNOS regions in the United States[29].

DISCUSSION

In a nationwide cohort of liver recipients, we found that the number of transplants for ALD was stable between 2002 and 2012, but rose by approximately 177 transplants per year between 2013 and 2015. This increase was observed more in young recipients and in females and was incompletely explained by a decrease in transplants for HCV/ALD. There was a significant increase in 8 out 11 UNOS regions, and a decrease only in region 9. This increase in transplants for ALD has not been previously described.

Prior epidemiologic studies on the indication for liver transplant have shown stable to decreasing rates of transplants for ALD, but these studies were based on data collected before 2013[7,8]. However, a more recent study noted an increase in transplants for ALD in recent years, which is more rapid than that for NASH[9]. Population-based studies have shown an increase in heavy alcohol use[5], binge drinking[5] and per capita alcohol use[10] since the early 2000s. During the same time period, there was an increase in hospitalization for alcohol-related diagnosis and an increase in age-adjusted death rates from ALD[11,12]. Furthermore, the proportion of cirrhosis-related deaths attributable to alcohol have increased in young patients (25-54 years old)[12]. However, other data suggest decreasing overall prevalence of ALD in the population[9].

The reason for this increase in transplants for ALD starting in 2013 is uncertain. Our data suggest that the surge is not due to an increasing BMI in this population or an increase in transplants for acute alcoholic hepatitis,

Table 2 Temporal trends in characteristics of alcoholic liver disease liver transplant recipients

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	*P* value
n (% annual)	553 (12.8%)	597 (12.8%)	628 (12.4%)	688 (13.0%)	695 (12.7%)	660 (12.3%)	578 (11.1%)	608 (11.6%)	619 (11.7%)	651 (12.1%)	613 (11.4%)	685 (12.4%)	805 (13.9%)	1020 (16.5%)	
Age	53.0 ± 8.2	52.9 ± 8.5	54.0 ± 8.8	53.4 ± 8.6	53.7 ± 8.6	54.5 ± 8.7	53.6 ± 8.9	54.3 ± 8.5	54.1 ± 8.9	54.0 ± 8.9	53.6 ± 8.9	52.8 ± 9.4	53.7 ± 9.7	52.5 ± 10.2	0.1
Female	124 (22.4%)	126 (21.1%)	125 (19.9%)	134 (19.5%)	156 (22.4%)	133 (20.2%)	127 (22.0%)	146 (24.0%)	164 (26.5%)	170 (26.1%)	153 (25.0%)	172 (25.1%)	200 (24.8%)	280 (27.5%)	0.001
Race															0.03
Black	15 (2.7%)	16 (2.7%)	23 (3.7%)	24 (3.5%)	32 (4.6%)	19 (2.9%)	21 (3.6%)	22 (3.6%)	18 (2.9%)	37 (5.7%)	23 (3.8%)	35 (5.1%)	38 (4.7%)	48 (4.7%)	
Hispanic	71 (12.8%)	76 (12.7%)	76 (12.1%)	77 (11.2%)	98 (14.1%)	98 (14.8%)	95 (16.4%)	79 (13.0%)	85 (13.7%)	88 (13.5%)	93 (15.2%)	96 (14.0%)	103 (12.8%)	150 (14.7%)	
Other	6 (1.1%)	12 (2.0%)	13 (2.1%)	12 (1.7%)	9 (1.3%)	12 (1.8%)	16 (2.8%)	9 (1.5%)	20 (3.2%)	16 (2.5%)	13 (2.1%)	18 (2.6%)	17 (2.1%)	38 (3.7%)	
White	461 (83.4%)	493 (82.6%)	516 (82.2%)	575 (83.6%)	556 (80.0%)	531 (80.5%)	446 (77.2%)	498 (81.9%)	496 (80.1%)	510 (78.3%)	484 (79.0%)	536 (78.2%)	647 (80.4%)	784 (76.9%)	
BMI	27.7 ± 5.3	27.8 ± 5.2	27.7 ± 5.5	27.9 ± 5.4	27.7 ± 5.4	28.4 ± 5.5	27.9 ± 5.4	27.9 ± 5.4	28.0 ± 5.6	27.9 ± 5.5	28.1 ± 5.4	28.0 ± 5.3	27.8 ± 5.4	28.0 ± 5.5	0.3
Diabetes															< 0.001
None	433 (78.3%)	458 (76.7%)	493 (78.5%)	538 (78.2%)	548 (78.8%)	484 (73.3%)	440 (76.1%)	485 (79.8%)	487 (78.7%)	518 (79.6%)	509 (83.0%)	560 (81.8%)	659 (81.9%)	828 (81.2%)	
Any	103 (18.6%)	122 (20.4%)	116 (18.5%)	138 (20.1%)	134 (19.3%)	167 (25.3%)	131 (22.7%)	109 (17.9%)	127 (20.5%)	128 (19.7%)	100 (16.3%)	122 (17.8%)	144 (17.9%)	187 (18.3%)	
Unknown	17 (3.1%)	17 (2.8%)	19 (3.0%)	12 (1.7%)	13 (1.9%)	9 (1.4%)	7 (1.2%)	14 (2.3%)	5 (0.8%)	5 (0.8%)	4 (0.7%)	3 (0.4%)	2 (0.2%)	5 (0.5%)	
MELD	20.6 ± 8.4	21.6 ± 9.2	22.6 ± 9.5	22.6 ± 8.7	22.8 ± 8.5	23.9 ± 8.9	24.8 ± 9.0	25.1 ± 8.7	25.8 ± 9.4	26.1 ± 9.5	27.0 ± 9.3	27.5 ± 9.7	28.1 ± 9.6	28.9 ± 10.4	< 0.001
HCC in explant	58 (10.5%)	41 (6.9%)	51 (8.1%)	37 (5.4%)	44 (6.3%)	39 (5.9%)	30 (5.2%)	23 (3.8%)	18 (2.9%)	27 (4.1%)	24 (3.9%)	28 (4.1%)	23 (2.9%)	39 (3.8%)	< 0.001

BMI: Body mass index; HCC: Hepatocellular carcinoma.

and it is not solely due to reclassification of HCV/ALD transplants as ALD. There has been a steady increase in the number of new waitlistings for ALD, but the rate of rise of transplants since 2013 seems to exceed the rate of rise of listings[9]. Perhaps there has been a recent improvement in both the referral for transplant and wait-listing for patients with ALD, who have historically have lower rates of both referral[13,14] and waitlist[15]. The American Association for the Study of Liver disease revised the "Evaluation for Liver Transplantation in Adults Practice Guidelines" in 2005[16] and again 2013[17]. The 2005 Guidelines recommended "it is prudent to delay transplantation for a minimum of 3-6 mo of abstinence from alcohol." However, in the 2013 guidelines it was acknowledged that 6 mo of sobriety before referral "may result in deterioration of the patient's medical condition so that psychosocial or addiction requirements determined from the initial evaluation may not be achievable." While there is not a temporal relationship between this publication (March 2014) and our observed increased in transplants for ALD (start of 2013), the 2013 Guidelines may reflect a developing leniency of the abstinence requirement amongst transplant programs.

ALD is historically the second most common etiology for LT in the European Liver Transplant Registry at 33.6%, trailing only virus related cirrhosis. However, in the setting of treatment for HCV, ALD has become the leading indication for LT[18]. There has been a sustained increase in the proportion of transplants performed for ALD since the late-1980s, including 2013-2015. In a Nordic paper, the proportion of transplants for ALD remained relatively constant between 1994 and 2013[19].

Early identification of problematic alcohol use and reduction in drinking has the potential to change the pattern we have described. Only 10% of patients with drinking problems are identified by primary care providers, and under-diagnosis is common in teenagers[20]. Brief interventions in the primary care setting can result in reduced consumption and may subsequently reduce alcohol-related harm and mortality[21,22]. After a single course of treatment by a qualified alcohol counselor, abstinent rates are 17 to 33% and an additional 7% to 12% reduce their intake[23].

There are several simple screening tools for alcohol use that are designed to be highly sensitive and easy to use in the primary care setting. The CAGE questionnaire is a 4-question test with binary answers; two "yes" responses are considered a positive test and should prompt additional testing[24,25]. Alternatively, the more extensive alcohol use disorders identification test was developed by the World Health Organization and consists of ten questions with five possible answers and a focus on identification of heavy drinkers[26,27]. Another option is a single screening question "How many times in the past year have you had 5 (males) or 4 (females) or more drinks in a day?" with a cutoff of 8 times, and can also be used to accurately identify patients with unhealthy alcohol use with good discrimination[28]. The widespread use of electronic medical records make systematic implementation of well validated tools inexpensive and quite practical. This would follow the approach for identification of smoking using the electronic medical

Table 3 Changes in number of transplants per year for alcoholic liver disease by age group, gender and etiology

	Mean per year 2002-2012	Mean per year 2013-2015	Difference	Change	*P* value
Total	626.4	836.7	210.3	1.34	0.002
Age group (yr)					
18-30	4.3	14.3	10.1	3.35	0.003
31-40	40.7	84.0	43.3	2.06	0.001
41-50	170.5	219.7	49.1	1.29	0.005
51-60	264.5	314.3	49.8	1.19	0.040
61-70	138.4	195.0	56.6	1.41	0.010
71-83	7.9	9.3	1.4	1.18	0.500
Gender					
Female	141.6	217.3	75.7	1.53	0.001
Male	484.7	619.3	134.6	1.28	0.005
Etiology					
Alcoholic cirrhosis	619.5	827.0	207.5	1.33	0.002
Alcoholic hepatitis	6.8	9.7	2.8	1.42	0.580
HCV/ALD	274.4	183.7	-90.7	0.67	0.050

HCV: Hepatitis C virus; ALD: Alcoholic liver disease.

Table 4 Changes in number of transplants per year for alcoholic liver disease by UNOS region

UNOS region	Mean per year 2002-2012	Mean per year 2013-2015	Difference	Change	*P* value
1	28.5	37.3	8.8	1.31	0.09
2	86.0	120.3	34.3	1.40	0.01
3	103.4	142.7	39.3	1.38	0.02
4	54.1	75.7	21.6	1.40	0.05
5	75.5	117.3	41.8	1.55	0.003
6	13.0	24.7	11.7	1.90	0.001
7	83.1	89.0	5.9	1.07	0.32
8	33.6	52.3	18.7	1.56	0.002
9	43.4	28.3	-15.0	0.65	0.23
10	52.3	71.0	18.7	1.36	0.03
11	53.5	78.0	24.5	1.46	0.005

record. The potential for this approach on the prognosis of patients with ALD could be profound.

There were several limitations to our study. We examined only patients transplanted for ALD, not those listed for transplantation, so we are unable to determine whether the increase observed is due to an increasing listing for ALD or an increase in the proportion of waitlisted patients with ALD undergoing transplant. However, Goldberg *et al*[29] recently showed a steeper rate of rise for LTs for ALD than absolute number of new waitlistings, although both are increasing. Additionally, we were unable to further explore why all but three UNOS regions demonstrated an increase in transplants for ALD.

In conclusion, in this study we demonstrate a nationwide increase in the number of transplants per year for ALD beginning in 2013, particularly in young and female patients. The reason for this increase is unknown, but comes in the setting of widespread and increasing alcohol use and hospital admissions for ALD. Consideration should be given to the use of screening tools aimed at detecting alcohol use in the primary care setting to identify patients with problematic alcohol use and promote reduction in consumption in order to avoid harm.

ARTICLE HIGHLIGHTS

Research background

Liver transplantation (LT) has become a life-saving procedure for patients with irreversible liver diseases. One of the common causes of chronic liver disease for which LT is potentially life-saving is alcoholic liver disease (ALD).

Research motivation

Population-based studies have shown that there has been an increase in the prevalence of both heavy drinking and binge drinking.

Research methods

Authors conducted a retrospective cohort analysis of transplant recipients in the United Network for Organ Sharing Standard Transplant Analysis and Research file.

Research results

Between 2002 and 2015, ALD was the third leading indication for transplant after HCV and hepatocellular carcinoma. The total number of transplants performed for ALD increased from 553 (12.8% of the annual total) in 2002 to 1020 (16.5%) in 2015.

Research conclusions

A nationwide increase was noted in the number of transplants per year for ALD beginning in 2013, particularly in young and female patients. This comes in the setting of widespread and increasing alcohol use and hospital admissions for ALD.

Research perspectives

Consideration should be given to the use of screening tools aimed at detecting alcohol use in the primary care setting to identify patients with problematic alcohol use and promote reduction in consumption in order to avoid harm.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Reverse time-dependent effect of alphafetoprotein and disease control on survival of patients with Barcelona Clinic Liver Cancer stage C hepatocellular carcinoma

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Institutional review board statement: This is a retrospective study based on the revision of anonymous clinical data; no additional interventional procedures or drug was performed/administered to the study population. Therefore, no institutional review board approval was required.

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Abstract

AIM

To characterize the survival of cirrhotic patients with Barcelona Clinic Liver Cancer (BCLC) stage C hepatocellular carcinoma (HCC) and to ascertain the factors predicting the achievement of disease control (DC).

METHODS

The cirrhotic patients with BCLC stage C HCC evaluated by the Hepatocatt multidisciplinary group were subjected to the investigation. Demographic, clinical and tumor features, along with the best tumor response and overall survival were recorded.

RESULTS

One hundred and ten BCLC stage C patients were included in the analysis; the median overall survival was 13.4 mo (95%CI: 10.6-17.0). Only alphafetoprotein (AFP) serum level > 200 ng/mL and DC could independently predict survival but in a time dependent manner, the former was significantly associated with increased risk of mortality within the first 6 mo of follow-up (HR = 5.073, 95%CI: 2.159-11.916, P = 0.0002), whereas the latter showed a protective effect against death after one year (HR = 0.110, 95%CI: 0.038-0.314, P < 0.0001). Only patients showing microvascular invasion and/or extrahepatic spread recorded lower chances of achieving DC (OR = 0.263, 95%CI: 0.111-0.622, P = 0.002).

CONCLUSION

The BCLC stage C HCC includes a wide heterogeneous group of cirrhotic patients suitable for potentially curative treatments. The reverse and time dependent effect of AFP serum level and DC on patients' survival confers them as useful predictive tools for treatment management and clinical decisions.

Key words: Hepatocellular carcinoma; Cirrhosis; Barcelona Clinic Liver Cancer stage C; Alphafetoprotein; Disease control; Performance status; Survival

Core tip: Refining the prognosis of Barcelona Clinic Liver Cancer (BCLC) stage C hepatocellular carcinoma (HCC) is crucial to select patients that can get benefit from and be suitable for locoregional or surgical treatments. This study confirms that high alphafetoprotein serum level and DC are the best predictors of mortality for BCLC C patients, highlighting that the effect of these two variables is reverse and dynamic, in a time dependent manner. Outstandingly, performance status has not been found to be a strong predictor of mortality. According to our results, curative treatments should not be "a priori" excluded in a subset of BCLC stage C patients with favorable prognostic factors.

Ponziani FR, Spinelli I, Rinninella E, Cerrito L, Saviano A, Avolio AW, Basso M, Miele L, Riccardi L, Zocco MA, Annicchiarico BE, Garcovich M, Biolato M, Marrone G, De Gaetano AM, Iezzi R, Giuliante F, Vecchio FM, Agnes S, Addolorato G, Siciliano M, Rapaccini GL, Grieco A, Gasbarrini A, Pompili M. Reverse time-dependent effect of alphafetoprotein and disease control on survival of patients with Barcelona Clinic Liver Cancer stage C hepatocellular carcinoma. *World J Hepatol* 2017; 9(36): 1322-1331 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i36/1322.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i36.1322

INTRODUCTION

Hepatocellular carcinoma (HCC) has been recognized as a major health problem, as it ranks third among the leading causes of death due to cancer and is the sixth most common tumor with a worldwide occurrence[1].

While there are several options available for the treatment of HCC, their choice most likely depends on tumor stage, impairment of normal liver function, patient's performance status (PS) and comorbidities. The most widely accepted staging system for HCC is the Barcelona Clinic Liver Cancer (BCLC), which was based on the patients clinical features along with tumor-related variables and therefore categorized five different stages with progressively worsening prognosis and different treatment options[1,2].

The patients with an advanced HCC belong to the BCLC stage C, which includes tumors with macrovascular invasion, and/or extrahepatic spread

and/or mild cancer-related symptoms, PS 1-2 (Eastern Cooperative Oncology Group), and mild to moderate liver function impairment (Child-Pugh stage A-B). The only therapeutic option recommended for BCLC stage C HCC is the drug sorafenib, a multikinase inhibitor that has been reported to extend the overall survival of patients up to nearly 3 mo[3].

Given the higher number of heterogeneous and complex cases encountered in the field-practice, the BCLC classification is often not exhaustive, and the increasing number of new therapeutic options and their combinations makes difficult to strictly adhere to BCLC suggestions. This has been largely demonstrated in other categories of patients such as those belonging to the BCLC stage B group, who had not been subjected to transarterial chemoembolization (TACE), the treatment recommended by the BCLC algorithm, in more than one third of cases[4-6].

The BCLC stage C HCC encompasses a wide spectrum of tumors and patients' with different characteristics that may get benefit from and be suitable for locoregional or surgical treatments[7-9]. Nonetheless, in this stage too, the universal administration of sorafenib to the patients following the BCLC algorithm may sometimes be arguable and other therapeutic options could be explored according to patient's individual conditions.

The current study is principally aimed at characterizing the prognosis of cirrhotic patients with BCLC stage C HCC as assessed by a multidisciplinary team in an Italian tertiary care center. In addition to this, the other objective is the identification of the factors predicting the achievement of disease control (DC).

MATERIALS AND METHODS

The present study was performed at the Agostino Gemelli University Hospital, Rome, Italy. The prospective database of the Hepatocatt multidisciplinary group, containing clinical, tumor and outcome data of all liver cancer subjects evaluated in the seven years at our Institute was reviewed, and the cohort of cirrhotic patients with BCLC stage C HCC were selected as the prime object of the investigation.

The following criteria were adopted for the selection of patients: PS grade $\leqslant$ 2; Child-Pugh class A or B; tumor macrovascular invasion (mainly portal vein and/or hepatic veins and/or inferior vena cava); and/or extrahepatic spread. The HCC was diagnosed by multiphasic contrast-enhanced computed tomography (CT), gadolinium-enhanced magnetic resonance imaging (MRI) and/or by ultrasound-guided biopsy, as per the guidelines of European Association for the Study of the Liver and the American Association for the Study of Liver Diseases[1,2]. Based on the liver function and patients' characteristics, the modalities of HCC treatment were decided by the Hepatocatt multidisciplinary board, comprising of hepatologists, hepatobiliary and transplant surgeons, oncologists, radiologists, and pathologists. The imaging criteria (CT and/or MRI) for assessing the tumor response established by mRECIST were followed[10]. For individual patient, the treatment outcome was documented; DC was achieved in those patients who acquired a stable disease (SD), partial response (PR) or complete response (CR) as the best treatment outcome.

The patients' survival was the measure of success as primary outcome. The follow-up time was defined as the number of months from the entry in the BCLC stage C till their death or last visit. The factors that could predict the achievement of DC were also investigated as secondary endpoint.

Statistical analysis

Statistical analysis was performed using non-parametric tests due to the non normal distribution of data. The continuous variables were expressed as median and range, while the categorical variables as frequencies and percentages.

Pre-treatment variables [Child-Pugh score, PS, number and maximum size of HCC lesions, presence of macrovascular invasion or extrahepatic spread, alphafetoprotein (AFP) serum level, NIACE score value[11], and diabetes] and post-treatment variables (the number of treatments received after entry in the BCLC stage C and the achievement of DC) were considered as prognostic factors of patients' survival. The univariate analysis of survival estimates was performed using the Kaplan-Meier curve and the *log-rank* test was applied to check the differences between the groups. The variables with a $P < 0.100$ were included in the Cox proportional hazard regression model for the multivariate survival analysis, adjusting for gender and age.

The assumption of proportionality was confirmed by plotting the scaled Schoenfeld residuals over the time [log hazard ratio (beta) over time] and by performing a non-proportionality test (Pearson correlation test) for the overall model and for each covariate of the model. Interaction terms were subsequently introduced in the analysis for that factors that varied significantly over time. Fisher's exact test and binomial logistic regression were performed to identify the predictors of DC among pre- and post-treatment variables.

Statistical analysis was carried out using the R statistics program version 3.1.2. All statistical tests were two-sided and differences were considered significant at $P < 0.05$.

RESULTS

A total of 1030 records of liver cancer patients evaluated between May 2008 and May 2015 were reviewed, of which, 146 non-HCC liver tumors and 774 HCC in BCLC stage other than C (0, A, B or D) were disqualified from the study. Therefore, finally, 110 patients classified as BCLC stage C were included in the investigation. Clinical data and tumor characteristics of the study population are given in Table 1.

Table 1 Clinical and tumor characteristics of patients included in the study

Variable	Overall (110)
Age (yr)	67.5 (41-80)
Gender	
Male	91 (82.7)
Female	19 (17.3)
Etiology of liver disease	
Viral (HBV/HCV/HBV and HCV)	70 (63.6)
Alcohol	17 (15.5)
NASH/NAFLD	14 (12.7)
Viral and alcohol	9 (8.2)
PS	
0	33 (30)
1	64 (58.2)
2	13 (11.8)
Diabetes	
No	87 (79.1)
Yes	23 (20.9)
Child-Pugh score	
A	82 (74.5)
B	28 (25.5)
N nodules	
Single	35 (31.8)
2-3	20 (18.2)
> 3 or infiltrating	55 (50)
Maximum size	
⩽ 5 cm	56 (50.9)
> 5 cm	54 (49.1)
Macrovascular invasion	
No	60 (54.5)
Yes	50 (45.5)
Extrahepatic spread	
No	91 (82.7)
Yes	19 (17.3)
Macrovascular invasion and/or extrahepatic spread	
No	49 (44.5)
Yes	61 (55.5)
NIACE	
⩽ 3	84 (76.4)
> 3	26 (23.6)
AFP	
⩽ 200 ng/mL	74 (67.3)
> 200 ng/mL	36 (32.7)
Treatment before BCLC C diagnosis	
No	53 (48.2)
Yes	57 (51.8)
Type of treatment before BCLC C diagnosis (one or more per patient)	
TACE	35
Surgical resection	20
RFA	18
Sorafenib	13
PEI	11
TACE + RFA	8
TARE	4
DSM-TACE	1
Number of treatments after BCLC C diagnosis	
None	22 (20)
Single	32 (29.1)
Multiple	56 (50.9)
Type of treatment after BCLC C diagnosis (one or more per patient)	
Sorafenib	53
TACE	25
TARE	18
Second line systemic agent	15
PEI	12
DSM-TACE	5
LT	3
RFA	1
Best tumor response	
CR	10 (9.1)
PR	21 (19.1)
SD	12 (10.9)
PD	67 (60.9)
DC	
No	67 (60.9)
Yes	43 (39.1)

Continuous variables are reported as median value and range, categorical variables as frequencies and percentage. HBV: Hepatitis B virus; HCV: Hepatitis C virus; NASH: Nonalcoholic Steatohepatitis; NAFLD: Nonalcoholic fatty liver disease; PS: Performance status; AFP: Alphafetoprotein; DC: Disease control; TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization; DSM-TACE: Degradable starch microspheres transarterial chemoembolization; PEI: Percutaneous ethanol injection; RFA: Radiofrequency ablation; LT: Liver transplant; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; DC: Disease control.

Primary endpoint: Patients' survival

Out of 110 BCLC stage C patients included in the investigation, only 32 received a single treatment and 56 more than once, whereas 22 of them received only best supportive care due to the inadequate liver function. Sorafenib was the most common choice of treatment, followed by TACE, TARE, and second-line systemic agents in patients who were either intolerant to sorafenib or sorafenib failed for them (Table 1). In selected cases, PEI or RFA in combination with other treatments and DSM-TACE were also performed; three PS 1 patients without macrovascular invasion or extrahepatic spread and with tumors complying the Milan criteria after effective downstaging (when needed) underwent liver transplant (LT). The best-succeeded response was CR in 9.1% of cases, PR in 19.1%, SD in 10.9%, and PD in 60.9% of cases; overall, 43 (39.1%) patients obtained DC.

After a median follow-up of 22.9 mo (95%CI: 17.3-38.1), the cumulative median survival of the overall population was 13.4 mo (95%CI: 10.6-17.0, Figure 1). A total of 66 patients died and the most prevailing cause of death was attributed to tumor progression (50/66; 75.7%), followed by liver function failure (13/66; 19.7%), while in the remaining 3 patients, the death was caused by sepsis, post LT complications and bone fracture.

At univariate analysis, AFP serum level > 200 ng/mL, tumor size > 5 cm, the presence of macrovascular invasion, the presence of macrovascular invasion and/or extrahepatic spread as pre-treatment factors and the absence of DC as post-treatment factor were considered to be correlated with a worse outcome (Table 2). However, at the multivariate Cox regression, only AFP serum level > 200 ng/mL and DC were independent predictors of mortality (HR = 2.194, 95%CI: 1.249-3.855, P = 0.006 and HR = 0.190, 95%CI: 0.098-0.367, P < 0.0001, respectively). In particular, the effect of these two variables was reverse in a time dependent

Table 2 Univariate (Kaplan-Meier) and multivariate (Cox proportional hazard regression) survival analysis of patients with Barcelona Clinic Liver Cancer C hepatocellular carcinoma according to clinical and tumor variables

Variable	Univariate analysis		Multivariate analysis	
	Survival time (mo)	*P* value	Hazard ratio (95%CI)	*P* value
Age				
< 65 yr	13.9	0.903	-	-
⩾ 65 yr	13.8			
Gender				
Male	13	0.900	-	-
Female	14.2			
PS				
0	10.3	0.128	-	-
1/2	13.9			
Diabetes				
No	13	0.813	-	-
Yes	13.8			
Child-Pugh score				
A	13.4	0.957	-	-
B	12.8			
N nodules				
Single	13.8	0.776	-	-
2-3	13.4			
Multinodular/infiltrating	13			
Tumor size				
⩽ 5 cm	13.9	0.022[1]	1	0.275
> 5 cm	9.9		1.357 (0.784-2.349)	
Macrovascular invasion				
No	15.8	0.014[1]	1	0.866
Yes	9.5		1.095 (0.379-3.162)	
Extrahepatic spread				
No	11.2	0.274	-	-
Yes	6.7			
Macrovascular invasion and/or extrahepatic spread				
No	13.8	0.008[1]	1	0.429
Yes	6.3		1.547 (0.523-4.571)	
AFP				
⩽ 200 ng/mL	15.8	0.0002[1]	1	0.006[1]
> 200 ng/mL	6.3		2.194 (1.249-3.855)	
DC				
No	7.6	< 0.0001[1]	1	< 0.0001[1]
Yes	15.8		0.190 (0.098-0.367)	
NIACE score				
⩽ 3	13.8	0.515	-	-
> 3	6.7			

[1]Statistically significant results. PS: Performance status; AFP: Alpha-fetoprotein; DC: Disease control.

manner, as depicted by plotting the log hazard ratios (beta) over time (Figure 2). In the first 6 mo of follow-up, serum AFP > 200 ng/mL was directly associated with lower chances of survival, but the effect declined subsequently. Conversely, the favorable prognostic impact of DC curtailed in the early-intermediate period and became noticeable after 1 year of follow-up.

A term of interaction of these two covariates with time was then introduced in the Cox model and hazard

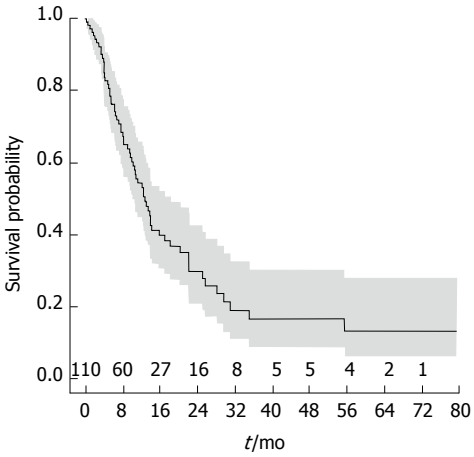

Figure 1 Cumulative survival of the overall cirrhotic patients with Barcelona Clinic Liver Cancer C stage hepatocellular carcinoma included in the study. The solid line shows the overall survival and the dotted lines the 95%CIs.

ratios were reported by each time interval (⩽ 6 mo, 7-12 mo, > 12 mo; Table 3). The AFP serum level > 200 ng/mL was significantly associated with higher risk of mortality within the first 6 mo of patients' entry into the BCLC stage C (⩽ 6 mo, HR = 5.073, 95%CI: 2.159-11.916, *P* = 0.0002). Conversely, DC exercised a significant protective effect in long-term phase (> 12 mo, HR = 0.110, 95%CI: 0.038-0.314, *P* < 0.0001).

There were also identified 5 patients who had unexpectedly longer survival (above the 95th percentile; median 63.3 mo). The characteristics of those subjects have been described in Table 4; outstandingly, in most of the cases (3/5) PS 1-2 was the major cause for categorizing them in BCLC stage C. Pre-treatment AFP serum level was ⩽ 200 ng/mL in all these patients; and two of them showed tumor macrovascular invasion without any extrahepatic spread. In one case Sorafenib, and in another TARE was prescribed; whereas, in the remaining three patients, curative treatments (LT), DSM-TACE or second-line systemic therapies were administered. Remarkably, DC was achieved in all these long-term survivors.

Secondary endpoint: DC

The examination of factors associated with DC was the second landmark of the study (Table 5). The patients who achieved DC (43/110; 39.1%) were illustrated by small-size tumors (> 5 cm: 13/43, 30.2% *vs* 41/67, 61.2%; *P* = 0.002), a lower frequency of macrovascular invasion (11/43, 25.6% *vs* 39/67, 58.2%; *P* = 0.0009), extrahepatic spread (3/43, 7% *vs* 16/67, 23.9%; *P* = 0.036) and of macrovascular invasion and/or extrahepatic spread (14/43, 32.6% *vs* 47/67, 70.1%; *P* = 0.0001), lower AFP serum level (> 200 ng/mL: 8/43, 18.6% *vs* 28/67, 41.8%; *P* = 0.013) and more frequently received at least one treatment (39/43, 90.7% *vs* 49/67, 73.1%; *P* = 0.029). However, only the presence of macrovascular

Table 3 Multivariate Cox regression model including alpha-fetoprotein and disease control as time dependent covariates

Variable	Multivariate analysis	
	Hazard ratio (95%CI)	*P* value
Macrovascular invasion		
No	1	0.917
Yes	1.066 (0.412-2.762)	
Macrovascular invasion and/or extrahepatic spread		
No	1	0.366
Yes	1.552 (0.584-4.124)	
Tumor size		
⩽ 5 cm	1	0.266
> 5 cm	1.369 (0.786-2.382)	
AFP (> 200 ng/mL *vs* ⩽ 200 ng/mL)		
< 6 mo	5.073 (2.159-11.916)	0.0002[1]
7-12 mo	0.948 (0.275-3.267)	0.932
> 12 mo	1.698 (0.620-4.648)	0.303
DC (Yes *vs* No)		
< 6 mo	0.220 (0.075-0.650)	0.096
7-12 mo	0.463 (0.181-1.189)	0.109
> 12 mo	0.110 (0.038-0.314)	< 0.0001[1]

For all other variables single hazard ratios were reported. [1]Statistically significant results. AFP: Alphafetoprotein; DC: Disease control.

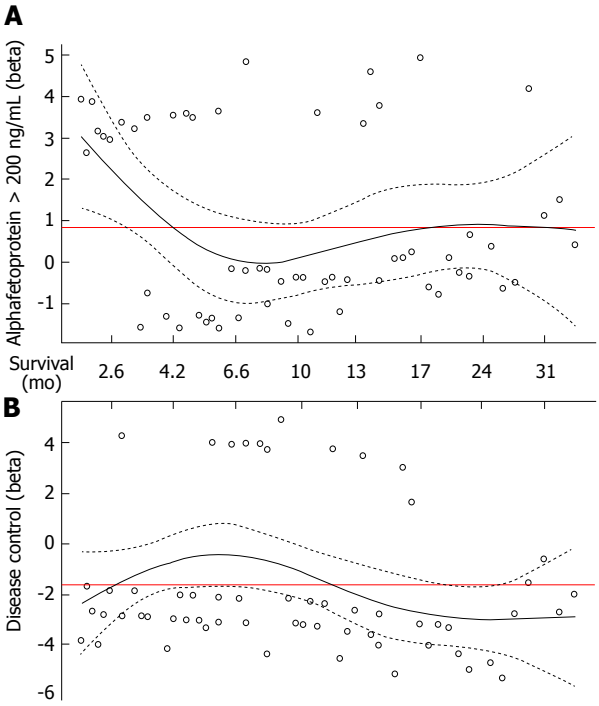

Figure 2 Plot of the scaled Schoenfeld residuals over time for alpha-fetoprotein serum level > 200 ng/mL (A) and disease control (B). The solid line shows the log of hazard ratio (beta) as a function of survival time with the 95%CI (dotted lines). The average beta value obtained at the Cox model without any time-adjustment is also reported (solid red line).

invasion and/or extrahepatic spread was independently associated with reduced likelihoods of achieving DC (OR 0.263, 95%CI: 0.111-0.622, *P* = 0.002). It is important to mention that among the 61 patients who showed macrovascular invasion and/or metastases, 44 (72.1%) received treatment and this proportion was significantly lower than that of patients showing intrahepatic disease without vascular involvement (44/49, 89.8%, *P* = 0.029).

DISCUSSION

The BCLC staging system is the most widely used approach for the therapeutic and prognostic classification of cirrhotic patients with HCC. While exploring the implementation of biomarker research in clinical practice to stratify tumors based on their biological aggressiveness[11], several sub-classifications of the BCLC stages consistent with prognostic factors and new scores have been proposed to improve the predictive power of this algorithm[12-14]. A more detailed stratification system based on the life expectancy may avoid offering treatments having a poor impact on patients' prognosis and often impairing the quality of life. These considerations are extremely important with regard to the selection of patients for the clinical trials of first or second line novel systemic agents.

The present study was aimed at investigating the predictors of survival in cirrhotic patients with BCLC stage C HCC and at assessing their effect in a time dependent manner. At the preliminary survival analysis, AFP serum level > 200 ng/mL and DC were found to be independent predictors of mortality (HR = 2.194, *P* = 0.006 and HR = 0.190, *P* < 0.0001, respectively).

Hence, the first finding of our report confirms high AFP serum level as a negative predictive marker in patients with advanced HCC and its impact on survival irrespective of the tumor stage at the time of diagnosis[15-20]. Furthermore, although this category of patients is classified as "advanced stage", we demonstrated a promising impact of the response to treatment, as shown by DC, on prognosis. Based on these findings, curative and locoregional treatments should not be "a priori" excluded in a subset of BCLC stage C patients with favorable predictive factors. As reported previously, surgical resection and LT can extend patients' survival in the BCLC stage C also[4-6,8,9,21], which supports the need of a novel method of prediction more customized to the specific patient. The identification of 5 long-term survivors (median 63.3 mo), where 3 were included in this stage only at impaired PS (1 or 2) in absence of vascular invasion or extrahepatic tumor spread, confirms the heterogeneity of patients included in the BCLC stage C and the benefits they got in terms of DC. In four patients, locoregional treatments were feasible and two of them were subjected to LT successfully. As already reported[22], the provision based on PS used in the BCLC algorithm is questionable. Furthermore, PS scores are subjective measures with high inter-observer variability, and it is often difficult to correctly evaluate tumor-related symptoms in patients already presenting compromised general conditions. In the current study, PS has not been found to be an independent predictor of survival, and this supports the hypothesis that alone it cannot be considered as an

Table 4 Characteristics of the 5 patients with long-survival (median 63.3 mo)

PT	Gender	Age	Etiology	PS	Child-Pugh	AFP > 200 ng/mL	No. of nodules	Maximum size	Macrovascular invasion	Extrahepatic spread	Diabetes	Pre-BCLC C treatments	Post-BCLC C treatments	Best response	DC	Survival (mo)	Status
PT3	M	65	HBV	1	A	No	Infiltrating	Infiltrating	Yes	No	No	None	Sorafenib	CR	Yes	79.4	Alive
PT10	M	73	HCV	1	A	No	> 3	18	No	No	No	TACE, resection, sorafenib	Second line systemic agent, DSM-TACE (2)	SD	Yes	63.3	Alive
PT27	M	58	HBV	2	B	No	2	19	No	No	No	RFA, TACE	LT	CR	Yes	67.1	Alive
PT53	M	63	Alcohol	1	B	No	> 3	50	No	No	No	None	TACE (4), TACE + RFA (1), LT	CR	Yes	58.9	AliVe
PT54	M	65	HCV	0	A	No	Single	40	Yes	No	Yes	None	TARE (2)	SD	Yes	38.1	Alive

HBV: Hepatitis B virus; HCV: Hepatitis C virus; PS: Performance status; BCLC: Barcelona Clinic Liver Cancer; AFP: Alphafetoprotein; TACE: Transarterial chemoembolization; RFA: Radiofrequency ablation; DSM-TACE: Degradable starch microspheres transarterial chemoembolization; LT: Liver transplant; TARE: Transarterial radioembolization; CR: Complete response; SD: Stable disease; DC: Disease control.

exclusion criterion for curative treatments. Outstandingly, the majority of the patients (88.2%) in our series showed a PS 0 or 1, and therefore, only a small subgroup of patients (11.7%) fell in PS 2 class, and that may have influenced the overall survival insignificantly. However, the non-homogeneity of PS stages among BCLC C patients may be attributed to the sequential enrollment of the subjects included in the analysis rather than a selection-bias, and gives a better understanding of what happens in the real field practice.

The novel finding surfaced out from our study is the dynamic influence of AFP serum level and DC on survival period (Figure 2). In particular, the log curve of the hazard ratio for AFP serum level > 200 ng/mL elevated at high beta points implying a direct correlation with mortality, but declined steadily over time. This was more evident during the early follow-up (within 6 mo), which reached the zero point and then increased slightly afterwards, and finally became constant in the later stage. The DC beta value showed an inverse tendency, being constantly negative and increasing towards the zero point at about 6 mo of follow-up; however, it decreased significantly after the first year. At the Cox regression model including time-dependent coefficients, the most noticeable prognostic effect of AFP appeared in the early follow-up period, with 83.5% probability of mortality during the first 6 mo of follow-up of patients with AFP serum level > 200 ng/mL compared to those with a lower value (HR 5.073, 95%CI: 2.159-11.916, $P = 0.0002$). On the other hand, the DC was found to be defensive against death, as evident especially in the long-term follow-up (> 12 mo, HR 0.110, $P < 0.0001$). This type of dynamic behavior of prognostic factors has not been documented earlier during the establishment of HCC, while for other malignancies, such as breast, lung, and colorectal cancer, it has already been described. Time-dependent analysis has allowed to model patients' survival more precisely, considering the dynamic behavior of mortality risk factors and pointing out the reverse effect of AFP serum level and DC on prognosis temporally. Our findings, therefore, emphasize that tumor biological aggressiveness remains the most important short time prognostic indicator whereas in the long term, the achievement of DC is very decisive to ameliorate patients' survival expectancy. This further supports the efforts towards improving the therapy management and also implementing the treatment options in the BCLC algorithm for stage C patients. Nevertheless, since high AFP serum level is associated with an increased risk of early mortality, the trials assaying new systemic agents or second line therapies should be very careful in selecting the patients, and consequences should be evaluated optimally based on the stratification of the biological aggressiveness.

The second milestone of our study was to identify predictive factors of DC. The presence of macrovascular invasion and/or extrahepatic spread was found to be independently associated with a reduced likelihood of achieving DC (OR = 0.263, $P = 0.002$). The negative effect of tumor diffusion outside the liver or into the bloodstream on patients' prognosis is well known, as thoroughly discussed in previous reports[23-25], and this could be indirectly due to the inadequacy of the currently available treatments to control an aggressive disease in an effective and systemic manner. Nevertheless, in our study the 61 patients showing macrovascular invasion and/or extrahepatic spread received treatment with a lower frequency as compared to those with non-invasive tumors (44/61, 72.1% *vs* 44/49, 89.8%, $P = 0.029$). Due to the extensive tumor burden, in this subgroup of patients supportive care was taken more often and this may also be the reason for the reduced DC rates to some extent.

Table 5 Univariate (Fisher's exact test) and multivariate (binomial logistic regression) analysis of factors associated with the achievement of disease control in patients with Barcelona Clinic Liver Cancer C hepatocellular carcinoma

Variable	DC (43)	No DC (67)	Univariate analysis	Multivariate analysis	
			P value	Odds ratio (95%CI)	*P* value
Age					
< 65 yr	15	27	0.229	-	
⩾ 65 yr	28	40			
Gender					
Male	35	56	0.471	-	
Female	8	11			
PS					
0	37	60	0.06	-	
1/2	6	7			
Diabetes					
No	34	53	0.653	-	
Yes	9	14			
Child-Pugh score					
A	31	51	0.524	-	
B	12	16			
N nodules					
Single	13	22	0.078		
2-3	11	9		-	
Multinodular/infiltrating	19	36			
Tumor size					
⩽ 5 cm	30	26	0.006[1]	1	0.298
> 5 cm	13	41		0.617 (0.236-1.610)	
Macrovascular invasion					
No	32	28	0.0003[1]	-	-
Yes	11	39			
Extrahepatic spread					
No	40	51	0.02[1]	-	-
Yes	3	16			
Macrovascular invasion and/or extrahepatic spread					
No	29	20	< 0.0001[1]	1	0.002[1]
Yes	14	47		0.263 (0.111-0.622)	
AFP					
⩽ 200 ng/mL	35	39	0.008[1]	1	0.179
> 200 ng/mL	8	28		0.461 (0.169-1.258)	
NIACE score					
⩽ 3	34	50	0.502	-	
> 3	9	17			
Treatment after BCLC C diagnosis					
No	4	18	0.04[1]	1	0.270
Yes	39	49		0.531 (0.147-1.917)	

[1]Statistically significant results. PS: Performance status; AFP: Alpha-fetoprotein; DC: Disease control.

Recently, the NIACE score has been proposed as a useful tool for the prognostic sub-staging of BCLC stage C patients, as well as for the management of treatment and for the selection of patients in clinical trials[14]. Probably, the different biological characters of tumors encompassed in our investigation could have negatively affected the prognostic ability of the NIACE score. Indeed, only 14% of the patients in the NIACE study cohort had previously undergone a treatment for HCC, as compared to 51.8% of the patients in our series, and the prevalence of alcohol related liver disease was higher than in our series of patients (30% *vs* 15.5%).

A possible limitation of this study could be its retrospective nature, although this was partially overcome by the rigorous and prospective collection of clinical records by the multidisciplinary group. Despite of having limited the number of records included in the analysis, the inclusion of patients treated only at our Center has reduced biasness related to diverse modalities of treatment or imaging interpretation by radiologists at different Centers.

The liver function did not appear to have a significant impact on patients' prognosis in our analysis; probably, a high tumor-related mortality has overcome the impact of hepatic impairment on survival. However, this cannot be absolutely confirmed, as the number of patients with conserved liver function largely exceeded that of patients with more severe liver impairment (74.5% Child A *vs* 25.5% Child B class).

In conclusion, our data confirm that the BCLC stage C comprises a huge heterogeneous group of cirrhotic patients suitable for locoregional and potentially curative treatments. This is the first report highlighting the reverse

and time-dependent effect of AFP serum level and DC as prognostic factors in cirrhotic patients with advanced stage HCC. In the patients with pre-treatment AFP serum level > 200 ng/mL the risk of early death increases up to 80%, while the achievement of post-treatment DC, which is less likely in the presence of macrovascular invasion and/or extrahepatic tumor spread, suggests higher chances of long-term survival. The combination of these predictive factors may be helpful in the sophistication of patients' prognosis, thereby being valuable in the selection of patients suitable for clinical trials and in designing the therapeutic strategy.

ARTICLE HIGHLIGHTS

Research background

Barcelona Clinic Liver Cancer (BCLC) stage C hepatocellular carcinoma (HCC) includes a heterogeneous group of patients with different clinical and tumor characteristics and survival expectancy, for whom sorafenib is the only recommended treatment option. The present study investigates the outcome of BCLC C patients who underwent different locoregional, surgical or systemic treatments.

Research motivation

To better stratify the prognosis of patients with BCLC C stage HCC.

Research objectives

To characterize the prognosis of cirrhotic patients with BCLC stage C HCC as assessed by a multidisciplinary team in an Italian tertiary care center and to identify those factors predicting the achievement of disease control (DC).

Research methods

The prospective database of the Hepatocatt multidisciplinary group, containing clinical, tumor and outcome data of all liver cancer subjects evaluated in the seven years at our Institute was reviewed.

Research results

The study confirms that the BCLC stage C comprises a huge heterogeneous group of cirrhotic patients suitable for locoregional and potentially curative treatments. Moreover, this is the first report highlighting the reverse and time-dependent effect of alphafetoprotein (AFP) serum level and DC as prognostic factors in cirrhotic patients with advanced stage HCC.

Research conclusions

The novel finding surfaced out from our study is the dynamic influence of AFP serum level and DC on survival period. In particular, the AFP serum level > 200 ng/mL was significantly associated with higher risk of mortality within the first 6 mo of patients' entry into the BCLC stage C; conversely, DC exercised a significant protective effect in long-term phase. Our report also highlight that the presence of macrovascular invasion and/or extrahepatic spread is independently associated with a reduced likelihood of achieving DC. Based on these findings, curative and locoregional treatments should not be "a priori" excluded in a subset of BCLC stage C patients. Indeed, predictive factors may be helpful in the sophistication of patients' prognosis, thereby being valuable in the selection of patients suitable for clinical trials and in designing the therapeutic strategy.

Research perspectives

Given the higher number of heterogeneous and complex cases encountered in the field-practice, the BCLC classification is often not exhaustive, and the increasing number of new therapeutic options and their combinations makes difficult to strictly adhere to BCLC suggestions. New algorithms for the stratification of patients' prognosis are needed to improve clinical practice.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Hospital contacts with alcohol problems prior to liver cirrhosis or pancreatitis diagnosis

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Abstract

AIM

To evaluate prior hospital contacts with alcohol problems in patients with alcoholic liver cirrhosis and pancreatitis.

METHODS

This was a register-based study of all patients diagnosed with alcoholic liver cirrhosis or pancreatitis during 2008-2012 in Denmark. Hospital contacts with alcohol problems (intoxication, harmful use, or dependence) in the 10-year period preceding the diagnosis of alcoholic liver cirrhosis and pancreatitis were identified.

RESULTS

In the 10 years prior to diagnosis, 40% of the 7719 alcoholic liver cirrhosis patients and 40% of the 1811

alcoholic pancreatitis patients had at least one prior hospital contact with alcohol problems. Every sixth patient (15%-16%) had more than five contacts. A similar pattern of prior hospital contacts was observed for alcoholic liver cirrhosis and pancreatitis. Around 30% were diagnosed with alcohol dependence and 10% with less severe alcohol diagnoses. For the majority, admission to somatic wards was the most common type of hospital care with alcohol problems. Most had their first contact with alcohol problems more than five years prior to diagnosis.

CONCLUSION

There may be opportunities to reach some of the patients who later develop alcoholic liver cirrhosis or pancreatitis with preventive interventions in the hospital setting.

Key words: Alcoholic liver disease; Alcoholic pancreatic disease; Nationwide; Prevention; Hospital contacts

Core tip: Alcohol-related liver and pancreatic disease are preceded by many years of heavy drinking. Hospital contacts with obvious alcohol problems prior to development of alcohol-related liver or pancreatic disease may constitute opportunities for prevention if alcohol problems were to be consistently managed. In this study of all Danish alcoholic liver cirrhosis and alcoholic pancreatitis patients, forty percent had at least one previous hospital contact with obvious alcohol problems in the 10 years prior to diagnosis. Most of these patients had their first contact with alcohol problems more than five years prior to diagnosis.

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INTRODUCTION

Alcohol is the single most important cause of liver and pancreatic disease in Western countries[1,2]. Alcohol-related liver and pancreatic disease are associated with a considerably mortality risk[3,4], preceded by years of heavy drinking[5,6]. However, among hazardous drinkers reducing or abandoning alcohol consumption can attenuate the risk of full blown disease or death due to alcohol-related liver and pancreatic disease[2,7,8]. Since these diseases develop over many years prior to diagnosis, this offers a window of opportunity in which preventive interventions could be implemented.

Hospital contacts with alcohol problems in the period before disease may constitute opportunities for offering alcohol treatment[9,10]. Such hospital contacts include those involving alcohol intoxication (a marker of excessive drinking), harmful alcohol use (a diagnosis used for mild cases of alcohol dependence or when the alcohol use has caused physical or mental disease), and alcohol dependence in more severe cases of alcohol problems[11,12]. In Denmark[13], as in many other countries[14-16], formalised hospital-based alcohol treatment is not available. For example, patients admitted with alcohol withdrawal will be discharged when acute symptoms have been alleviated, without the development of further treatment for underlying alcohol misuse or dependence.

We recently found that patients with hospital contacts with alcohol problems had a more than 10-fold greater rate of alcoholic liver cirrhosis compared to the general population[17]. In the present study, the reverse situation was evaluated; the extent to which patients with alcoholic liver cirrhosis or alcoholic pancreatitis have prior hospital contacts with alcohol problems. Earlier studies found that 33%-58% of liver cirrhosis patients had prior hospital contacts indicated by disorders that are sometimes, though not always, associated with alcohol problems such as injuries, non-variceal upper gastrointestinal bleeding, and epilepsy[18-20]. Hospital contacts with a more specific set of alcohol problems, however, might represent a more feasible opportunity to offer alcohol treatment.

We conducted a nationwide study of all patients who were diagnosed with alcoholic liver cirrhosis and alcoholic pancreatitis 2008 to 2012 in Denmark. In these patients, we evaluated the extent of prior hospital contacts with alcohol problems in the 10 years prior to their diagnosis of alcoholic liver cirrhosis or alcoholic pancreatitis.

MATERIALS AND METHODS

Data sources

The study was based on Danish nationwide registries. All Danish citizens have access to free healthcare. The National Patient Register contains data on all somatic hospital admissions since 1977[21]. From 1995 contacts with emergency rooms, outpatient clinics, and psychiatric hospital were recorded. The Danish Register of Causes of Death has recorded causes of death among all Danish citizens since 1970[22]. In all registries, diagnoses are recorded according to the 8th (1971-1993) and 10th (1994-present) revision of the international classification of diseases (ICD)[21].

Information on vital status, civil status, and migration to and from Denmark was obtained from the Danish Civil Registration System and education from Statistics Denmark[23]. The registries were linked by a personal identification number, a identifier assigned to all Danish residents at birth since 1968[23].

Study population

The study population consisted of all patients with a first diagnosis of alcoholic liver cirrhosis or alcoholic pancreatitis in Denmark from 2008 to 2012 (alcoholic liver cirrhosis; ICD-8: 571.0 and ICD-10: K70.3, K70.4 and alcoholic pancreatitis; ICD-10: K85.2, K86.0). Patients diagnosed with alcoholic liver cirrhosis or alcoholic pancreatitis from 1977, when The National Patient Register was initiated, to 2008 were therefore excluded. We combined acute and chronic alcoholic pancreatitis since they are often found together and are both preceded by years of heavy drinking[2,7]. In Denmark, there are restrictions on alcohol sale for young people less than 16-18 years. To ensure 10 years of follow-back before the diagnosis, we excluded patients less than 28 years of age at diagnosis (n = 27). Information from The National Patient Register and Danish Register of Causes of Death were combined. The patients not diagnosed during life but with alcoholic liver cirrhosis or alcoholic pancreatitis as their cause of dead were included. Patients diagnosed with alcoholic liver cirrhosis and alcoholic pancreatitis on the same day (n = 65) were assigned to the alcoholic liver cirrhosis group due to the higher mortality associated with this disease[3,24].

Comorbidity was assessed according to the Charlson Comorbidity Index score based on diagnoses made in the course of hospital contacts in the 10 years prior to diagnosis[25]. Psychiatric comorbidity was measured as the number of the following psychiatric diseases (ICD-10 codes): Dementia and organic disorders not caused by alcohol (F00-09), schizophrenia (F20-29), mood disorders (F30-39), neurotic and stress-related (F40-49), behavioural syndromes associated with physiological disturbances (F50-59), personality disorders (F60-69), mental retardation (F70-79), disorders of psychological development (F80-89), and behavioural and emotional disorders (F90-99)[11].

Prior hospital contacts with alcohol problems

A prior hospital contact with alcohol problems [alcohol intoxication (ICD-10: F10.0), harmful alcohol use (ICD-10: F10.1), or alcohol dependence (ICD-10: F10.2, F10.3, F10.4, F10.5)] was restricted to those occurring in the 10 years before the diagnosis of alcoholic liver cirrhosis or alcoholic pancreatitis. However, contacts occurring in the three months prior to diagnosis were excluded to avoid including hospital contacts that might have been precipitated by symptoms of liver or pancreatic disease that were not immediately recognised. A maximum of one hospital contact with alcohol problems per day was included.

Statistical analysis

Analyses were carried out separately for patients diagnosed with alcoholic liver cirrhosis and alcoholic pancreatitis. We did not calculate confidence limits since we had nationwide data[26]. Assessment of comparability of demographic and medical characteristics between patients with and without prior hospital contacts with alcohol problems were performed using χ^2 test for categorical data and t-test for continuous data on age, which followed a normal distribution. Alcohol diagnoses (alcohol intoxication, harmful alcohol use, and alcohol dependence) were assessed as an indicator of the severity of alcohol problems among patients with alcoholic liver cirrhosis and alcoholic pancreatitis[12]. We also estimated the type of hospital care of the prior hospital contacts with alcohol problems (somatic, psychiatric, inpatient, emergency room, or outpatient clinic). Finally, we estimated the time in years that had passed from the initial hospital contact with alcohol problems to alcoholic liver cirrhosis or pancreatitis diagnosis. All analyses were carried out in SAS version 9.4.

RESULTS

From 2008 to 2012, 7719 patients were diagnosed with alcoholic liver cirrhosis and 1811 were diagnosed with alcoholic pancreatitis in Denmark. Of patients with alcoholic liver cirrhosis, 3058 (40%) had at least one hospital contact with alcohol problems within the prior 10 years excluding the three months prior to diagnosis (Table 1). The equivalent number was 719 (40%) for patients with alcoholic pancreatitis. In both patient groups, those with prior hospital contacts with alcohol problems were younger, more often men, more often married, and more often had somatic and psychiatric disease compared to those with no such contacts. For example, of patients with alcoholic liver cirrhosis with prior hospital contacts with alcohol problems, 2217 (72%) had no psychiatric comorbidity, 522 (17%) one, and 319 (10%) had two or more. In alcoholic liver cirrhosis patients without prior hospital contacts with alcohol problems, these numbers were 4394 (94%), 203 (4.6%) and 64 (1.4%).

The number of patients not diagnosed during life but having alcoholic liver cirrhosis and alcoholic pancreatitis as their cause of death were 875 (11%) and 106 (5.9%).

Number of prior hospital contacts with alcohol problems

The 7719 patients with alcoholic liver cirrhosis had a total of 38227 hospital contacts with alcohol problems in the prior 10-years (mean of 5.0 contacts). The median number (5^{th}-95^{th} percentiles) of prior contacts was 0 (0-19). The 1811 patients with alcoholic pancreatitis had 8997 prior hospital contacts with alcohol problems in the prior 10 years (mean of 5.0 contacts). The median number (5^{th}-95^{th} percentiles) of prior contacts was also 0 (0-19) in these patients.

Whereas 60% of the alcoholic liver cirrhosis patients had no prior hospital contacts with alcohol problems in the prior 10 years, 902 (12%) had one, 992 (13%) had two to four, 509 (7.0%) had five to nine, and 650 (8.0%) had ten or more (Figure 1). The percentages were similar in patients with alcoholic pancreatitis.

Table 1 Demographic and medical characteristics among patients newly diagnosed with alcoholic liver cirrhosis or alcoholic pancreatitis 2008-2012 in Denmark according to a prior hospital contact with alcohol problems within 10 years *n* (%)

Characteristic	Alcoholic liver cirrhosis (*n* = 7719)			Alcoholic pancreatitis (*n* = 1811)		
	Yes	No	*P* value	Yes	No	*P* value
Cohort, *n*	3058 (40)	4661 (60)		719 (40)	1092 (60)	
Age, mean (range)	57 (29-92)	61 (28-93)	< 0.0001	53 (28-90)	58 (28-92)	< 0.0001
Sex, men	2144 (70)	3159 (68)	0.03	562 (78)	810 (74)	0.05
Civil status, married	1338 (44)	1681 (36)	< 0.0001	289 (40)	345 (32)	0.000
Education (yr)			0.001			0.38
⩽ 9	1479 (48)	2062 (44)		342 (48)	483 (44)	
9-11	1170 (38)	1950 (42)		297 (41)	481 (44)	
⩾ 12	409 (14)	649 (14)		80 (11)	128 (12)	
Charlson comorbidity index			< 0.0001			0.02
0	938 (31)	1890 (41)		263 (36)	472 (43)	
1-2	1201 (39)	1402 (30)		285 (40)	391 (36)	
⩾ 3	919 (30)	1369 (29)		171 (24)	229 (21)	
Number of psychiatric comorbidities			< 0.0001			< 0.0001
0	2217 (73)	4394 (94)		478 (67)	990 (91)	
1	522 (17)	203 (4.6)		139 (19)	68 (6.0)	
⩾ 2	319 (10)	64 (1.4)		102 (14)	34 (3.0)	

Values are numbers (percentages) unless otherwise stated, *n* = 9530.

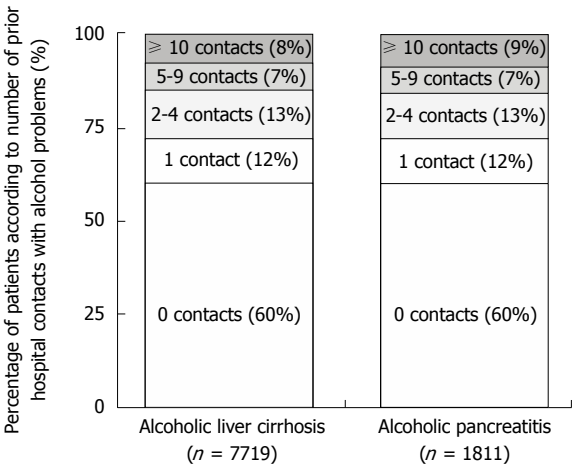

Figure 1 Number of hospital contacts with alcohol problems in the prior 10 years among patients newly diagnosed with alcoholic liver cirrhosis or alcoholic pancreatitis 2008-2012 in Denmark. Values are percentages of patients (*n* = 9530).

Alcohol diagnoses and type of hospital care of prior hospital contacts with alcohol problems

Nearly a third of patients with alcoholic liver cirrhosis and alcoholic pancreatitis had a diagnosis of alcohol dependence when hospitalized with alcohol problems in the prior 10 years (Table 2). Only 10% had less severe alcohol diagnoses of harmful alcohol use (6.7%-7.5%) or alcohol intoxication (2.3%-2.5%).

More patients had been admitted to a somatic hospital (36%) with alcohol problems than to a psychiatric hospital (15%-16%) in the 10 years prior to diagnosis. Admission to somatic wards with alcohol problems was the most common type of hospital care, which accounted to 2051 (27%) of patients with alcoholic liver cirrhosis and 509 (28%) of patients with alcoholic pancreatitis.

Time between the initial hospital contact with alcohol problems and diagnosis

In those patients diagnosed with alcoholic liver cirrhosis who had a prior hospital contact with alcohol problem, more than half had it at least five years before their diagnosis (Figure 2). Only 340 (4%) of all alcoholic liver cirrhosis patients had an initial contact with alcohol problems in the year before diagnosis whereas 980 (14%) had it one two to four years before, 1312 (16%) five to nine years before, and in 426 (6%) ten years before. A similar pattern was seen for those diagnosed with alcoholic pancreatitis.

DISCUSSION

In the present study, 40% of all Danish patients with alcoholic liver cirrhosis and alcoholic pancreatitis diagnosed from 2008 to 2012 had at least one hospital contact with alcohol problems in the prior 10 years before diagnosis. Every sixth patient (15%-16%) had more than five contacts. The pattern of prior hospital contacts with alcohol problems was similar for patients diagnosed with alcoholic liver cirrhosis and alcoholic pancreatitis. Roughly 30% had been given a prior diagnosis of alcohol dependence and 10% had less severe alcohol diagnoses (harmful use and intoxication). Inpatient admission to a somatic ward was the type of hospital care most patients have had with prior alcohol problems. More than half of cases with a prior hospital contact in the preceding 10 years had had their initial alcohol-related contact five or more years prior to diagnosis.

This study has a number of strengths. It covers

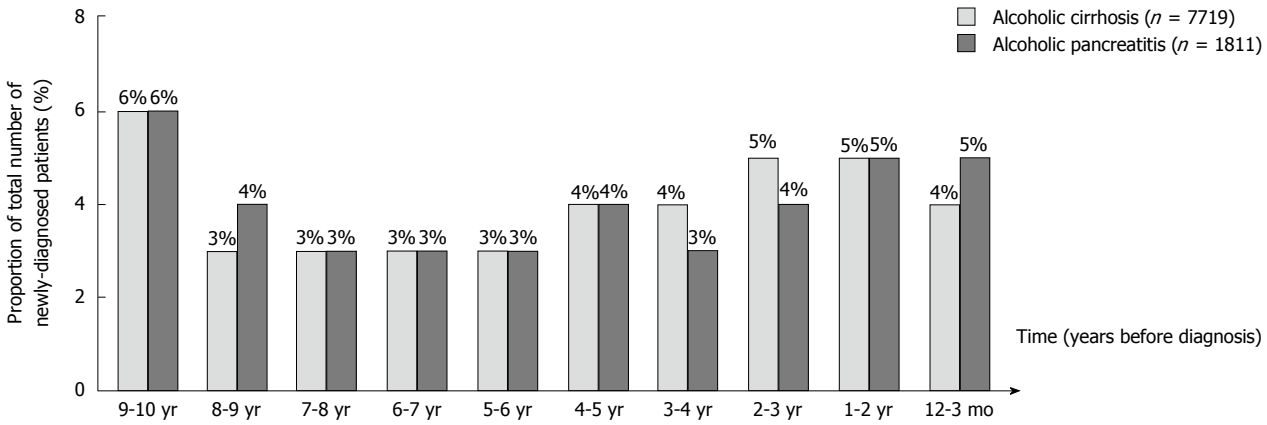

Figure 2 Years between initial hospital contact with alcohol problems and alcoholic liver cirrhosis or pancreatitis diagnosis among patients newly diagnosed with alcoholic liver cirrhosis or alcoholic pancreatitis 2008-2012 in Denmark. Values are percentages of patients (*n* = 9530).

Table 2 Most severe alcohol diagnosis recorded and types of hospital care of prior hospital contacts with alcohol problems within 10 years, among patients newly diagnosed with alcoholic liver cirrhosis or alcoholic pancreatitis 2008-2012 in Denmark

	Alcoholic liver cirrhosis (*n* = 7719)	Alcoholic pancreatitis (*n* = 1811)
Prior hospital contact with alcohol problems		
No	4661 (60)	1092 (60)
Yes	3058 (40)	719 (40)
If yes, the most severe alcohol problem diagnosis recorded		
Intoxication	184 (2.3)	46 (2.5)
Harmful use	527 (6.7)	141 (7.8)
Dependence	2347 (31)	532 (30)
If yes, types of hospital care[1]		
Somatic hospital	2743 (36)	644 (36)
Somatic ward	2051 (27)	509 (28)
Somatic emergency room	970 (13)	226 (12)
Somatic outpatient clinic	1150 (15)	250 (14)
Psychiatric hospital	1157 (15)	294 (16)
Psychiatric ward	454 (5.9)	126 (7.0)
Psychiatric emergency room	775 (10)	192 (11)
Psychiatric outpatient clinic	431 (5.6)	125 (6.9)

[1]Patients counted in several categories if they had more than one prior hospital contact with alcohol problems with different types of hospital care. Values are numbers (percentages) of patients (*n* = 9530).

the entire Danish population for which there is almost complete data on hospital care[21], and cause of death[22]. The alcoholic liver cirrhosis diagnosis in the registry has a high positive predictive value of correctly specifying liver cirrhosis: 78%-92% when compared to information from liver biopsies or clinical evaluation[27,28]. The validity of the alcoholic pancreatitis diagnosis has not been evaluated, but since this diagnosis is managed by gastroenterology specialists in Denmark, we expect the validity to be high[4]. A potential limitation is the validity of the classification of hospital contacts with alcohol problems. These diagnoses are most likely underreported leading to an underestimation of prior hospital contacts with alcohol problems[29].

Prior studies of cirrhosis patients found that 33%-58% had prior health care attendances with disorders that are sometimes associated with alcohol problems[18,20]. This is in accordance with our study where 40% of alcoholic cirrhosis patients had prior hospital contacts with alcohol problems. Our finding that some of the patients with alcohol problems have a considerably high number of repeated contacts due to alcohol has been reported before[12]. To our knowledge, no other study has assessed alcohol problems in patients with alcoholic pancreatitis.

The proportion of alcoholic liver cirrhosis patients with alcohol problems and the severity of these problems found in our study are in line with results from questionnaire-based studies[30-32]. These studies found roughly one third of patients to be moderate or severely alcohol dependent, one third mildly dependent and one third not dependent[30-32]. This underscores the observation that alcoholic liver cirrhosis patients in general have a lower degree of alcohol problems than people seeking treatment for alcohol problems[31,33].

The majority of prior hospital contacts with alcohol problems were with somatic, not psychiatric hospitals.

This is likely to reflect the fact that the majority of these cases were precipitated by injuries or non-psychiatric comorbidity[19,20]. That most contacts were as ward admissions rather than emergency room indicate a higher level of disease severity needing longer observation or more complex treatment than could be offered in the emergency room. The relatively few outpatient contacts with alcohol problems might indicate a lower utilization of routine or preventive care in favour of acute hospital admissions when health problems have become more severe, which was observed in heavy drinkers of old age[34].

Finally, in agreement with the long period of heavy drinking that commonly precedes the development of alcoholic liver cirrhosis and alcoholic pancreatitis[5,6,8], for the majority of patients in our study with prior alcohol contacts, more than five years had passed between their initial contact and diagnosis of alcoholic liver cirrhosis and pancreatitis.

The implication of our study is that there are opportunities to reach around half of patients who later develop alcoholic liver cirrhosis or alcoholic pancreatitis with preventive interventions in the hospital setting[9]. Suggested preventive interventions for liver disease involve implementation of hospital-based alcohol care teams which was shown to reduce alcohol-related admissions[9,35]. It may also involve non-invasive assessment of liver disease[36,37]. Hospital patients with alcohol problems and somatic disease or injury are in particular motivated for alcohol treatment[38-41].

Future studies should assess contacts with obvious alcohol problems in primary care in addition to hospital contacts to compare where patients are most frequently seen with alcohol problems prior to diagnosis of alcoholic liver cirrhosis or alcoholic pancreatitis[18,20,42].

About half of alcoholic liver cirrhosis and pancreatitis patients had hospital contacts with alcohol problems prior to diagnosis. There seems to be opportunities to reach some of the patients who later develop alcoholic liver cirrhosis or pancreatitis with preventive interventions in the hospital setting.

ARTICLE HIGHLIGHTS

Research background

Alcoholic liver cirrhosis and alcoholic pancreatitis develop over many years prior to diagnosis, which offers a window of opportunity in which preventive interventions could be implemented. Hospital contacts with alcohol problems in the period before disease may constitute opportunities for offering alcohol treatment. Earlier studies found that 33%-58% of liver cirrhosis patients had prior hospital contacts indicated by disorders that are sometimes, though not always, associated with alcohol problems such as injuries, non-variceal upper gastrointestinal bleeding, and epilepsy. Hospital contacts with a specific set of alcohol problems (alcohol intoxication, harmful alcohol use, and alcohol dependence) might represent a more feasible opportunity to offer alcohol treatment than disorders associated with alcohol problems. No prior studies evaluated hospital contacts with alcohol problems in patients with alcoholic pancreatitis.

Research motivation

In Denmark, as in many other countries, formalised hospital-based alcohol treatment is not available. Hospitalization with alcohol problems prior to alcoholic liver cirrhosis or pancreatitis diagnosis may represent an opportunity to offer preventive interventions. In a nationwide study, we evaluated previous hospital contacts with alcohol problems in patients with incident alcoholic liver cirrhosis and alcoholic pancreatitis diagnosis.

Research objectives

The objective was to conduct a nationwide study of all patients diagnosed with alcoholic liver cirrhosis and alcoholic pancreatitis 2008 to 2012 in Denmark. In these patients, the extent of prior hospital contacts with alcohol problems in the 10 years prior to their diagnosis of alcoholic liver cirrhosis or alcoholic pancreatitis were evaluated.

Research methods

This was a nationwide, register-based study of all patients diagnosed with alcoholic liver cirrhosis or pancreatitis during 2008-2012 in Denmark. Hospital contacts with alcohol problems (intoxication, harmful use, or dependence) in the 10-year period preceding the diagnosis of alcoholic liver cirrhosis or pancreatitis were identified. Data was obtained from nationwide registries on hospital contacts and causes of death. This is the first study to evaluate prior hospital contacts with alcohol problems in a nationwide design. Furthermore, no prior studies included psychiatric hospital contacts with alcohol problems. Hospital contacts with alcohol problems occurring in the three months prior to diagnosis of alcoholic liver cirrhosis and pancreatitis were excluded to avoid including hospital contacts that might have been precipitated by symptoms of liver or pancreatic disease that were not immediately recognised. Alcohol diagnoses (alcohol intoxication, harmful alcohol use, and alcohol dependence) were assessed as an indicator of the severity of alcohol problems among patients with alcoholic liver cirrhosis and alcoholic pancreatitis. We also estimated the type of hospital care of the prior hospital contacts with alcohol problems (somatic, psychiatric, inpatient, emergency room, or outpatient clinic). Finally, we estimated the time in years that had passed from the initial hospital contact with alcohol problems to alcoholic liver cirrhosis or pancreatitis diagnosis.

Research results

In the 10 years prior to diagnosis, 40% of the 7719 alcoholic liver cirrhosis patients and 40% of the 1811 alcoholic pancreatitis patients had at least one prior hospital contact with alcohol problems. Every sixth patient (15%-16%) had more than five contacts. The 7719 patients with alcoholic liver cirrhosis had a total of 38227 hospital contacts with alcohol problems in the prior 10-years (mean of 5.0 contacts). The median number (5^{th}-95^{th} percentiles) of prior contacts was 0 (0-19). The 1811 patients with alcoholic pancreatitis had 8997 prior hospital contacts with alcohol problems in the prior 10 years (mean of 5.0 contacts). The median number (5^{th}-95^{th} percentiles) of prior contacts was also 0 (0-19) in these patients. A similar pattern of prior hospital contacts was observed for alcoholic liver cirrhosis and pancreatitis. Around 30% were diagnosed with alcohol dependence and 10% with less severe alcohol diagnoses. For the majority, admission to somatic wards was the most common type of hospital care with alcohol problems. Most had their first contact with alcohol problems more than five years prior to diagnosis.

Research conclusions

In the present study, 40% of all Danish patients with alcoholic liver cirrhosis and alcoholic pancreatitis diagnosed from 2008 to 2012 had at least one hospital contact with alcohol problems in the prior 10 years before diagnosis. Every sixth patient (15%-16%) had more than five contacts. The pattern of prior hospital contacts with alcohol problems was similar for patients diagnosed with alcoholic liver cirrhosis and alcoholic pancreatitis. Roughly 30% had been given a prior diagnosis of alcohol dependence and 10% had less severe alcohol diagnoses (harmful use and intoxication). Inpatient admission to a somatic ward was the type of hospital care most patients have had with prior alcohol problems. More than half of cases with a prior hospital contact in the preceding 10 years had had their initial alcohol-related contact five or more years prior to diagnosis. The implication of our study is that there are opportunities to reach around half of patients who later develop alcoholic liver cirrhosis or alcoholic pancreatitis with preventive interventions in the hospital setting. Suggested preventive interventions for liver disease involve implementation of hospital-based alcohol care teams which was shown to reduce alcohol-related admissions. It may also

involve non-invasive assessment of liver disease. Hospital patients with alcohol problems and somatic disease or injury are in particular motivated for alcohol treatment.

Research perspectives

Future studies should assess contacts with obvious alcohol problems in primary care in addition to hospital contacts to compare where patients are most frequently seen with alcohol problems prior to diagnosis of alcoholic liver cirrhosis or alcoholic pancreatitis. In particular, randomized controlled trials are needed to evaluate if alcohol treatment in the hospital setting can decrease the incidence of alcoholic liver cirrhosis and alcoholic pancreatitis.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Efficacy and safety of sofosbuvir and ledipasvir in Japanese patients aged 75 years or over with hepatitis C genotype 1

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Abstract

AIM

To evaluate the efficacy and safety of a regimen containing sofosbuvir (SOF) and ledipasvir (LDV) in Japanese patients aged ⩾ 75 years with hepatitis C genotype 1.

METHODS

This multicenter, retrospective study consisted of 246 Japanese patients with HCV genotype 1 at nine centers in Miyazaki prefecture in Japan. Demographic, clinical, virological, and adverse effects (AE)-related data obtained during and after SOF/LDV therapy were collected from medical records. These patients were divided into two groups, younger (aged < 75 years) and elderly (aged ⩾ 75 years). Virological data and AEs were analyzed by age group.

RESULTS

The sustained virological response (SVR) rates at 12 wk after treatment were 99.2%, 99.4%, and 98.7% in the overall population and in patients aged < 75 and ⩾ 75 years, respectively. Common AEs during therapy were headache, pruritus, constipation, and insomnia. These occurred in fewer than 10% of patients, and their incidence was not significantly different between the younger and elderly groups. Two patients discontinued treatment, one due to a skin eruption and the other due to cerebral bleeding.

CONCLUSION

Compared with younger patients, elderly patients had a similar virological response and tolerance to SOF/LDV therapy.

Key words: Chronic hepatitis C; Sofosbuvir; Ledipasvir; Sustained virological response; Direct acting antivirals

Core tip: Most Japanese patients with hepatitis C are elderly, and those aged ⩾ 75 years account for more than 50%. However there are few reports regarding sofosbuvir (SOF) and ledipasvir (LDV) therapy in patients aged ⩾ 75 years in the real-world. The present study demonstrated that patients aged ⩾ 75 years had a similar virological response and tolerance to SOF/LDV therapy compared with patients aged < 75 years in the real-world cohorts. Therefore, SOF/LDV therapy might be effective and safe in elderly patients.

INTRODUCTION

Hepatitis C virus (HCV) infection is one of the major global causes of liver-related diseases such as chronic hepatitis, liver cirrhosis, liver failure, and hepatocellular carcinoma (HCC)[1,2]. In Japan, the prevalence of anti-HCV antibodies in the general population was estimated to be 0.9%[3], and significantly increased with age[3,4]. In fact, most Japanese patients with hepatitis C are elderly, and those aged ⩾ 75 years account for more than 50%[5]. However, elderly patients (⩾ 75 years) treated with interferon-based therapies have poor sustained virological response (SVR) rates and high discontinuation rates due to adverse effects (AEs)[6]. Moreover, in Japan the proportion of patients with HCV genotype 1 infection was found to 70%; most were reported to be infected with subgenotype 1b, compared to only approximately 1% with subgenotype 1a[7]. These population was known to exhibit treatment resistance with interferon (IFN) therapy[8], therefore novel anti-viral therapies for this population are urgently needed.

In 2014, the combination of daclatasvir (DCV), an NS5A inhibitor, and asunaprevir (ASV), an NS3/4A protease inhibitor, was the first interferon-free regimen to be approved for Japanese patients with HCV genotype 1[9]. Moreover, in 2015, the HCV NS5A inhibitor ledipasvir (LDV) and the HCV polymerase inhibitor sofosbuvir (SOF) were approved for this same population[10]. These regimens have demonstrated high efficacy with an improved safety profile and shorter treatment duration than interferon-based therapies[9,10]. However, patients aged ⩾ 75 years were excluded from these clinical trials[9,10], and therefore no data have been reported regarding the efficacy and safety of these regimens in this population. Recently, with respect to DCV/ASV therapy, several real-world studies showed that the SVR rate and discontinuation rate due to AEs were comparable in patients aged ⩾ 75 and < 75 years[11-13]. On the other hand, there are few reports regarding SOF/LDV therapy in patients aged ⩾ 75 years. Therefore, in the present study, we assessed the efficacy and safety of SOF/LDV therapy in Japanese patients aged ⩾ 75 years with hepatitis C genotype 1.

MATERIALS AND METHODS

Patients and therapy regimens

Between September 2015 and December 2016, 246 patients infected with HCV genotype 1 were treated with SOF/LDV at nine centers in Miyazaki prefecture in Japan. Demographic, clinical, virological and AE-related data obtained during and after therapy were retrospectively collected from medical records. Patients who had already received DCV/ASV therapy were excluded. Cirrhotic patients with Child-Pugh class B and C were excluded. Patients received 12 wk of treatment with a fixed-dose combination tablet containing 90 mg of LDV and 400 mg of SOF, administered orally once daily. In a phase 3 clinical trial in Japan, the addition of ribavirin to SOF/LDV did not improve the SVR12 rate, but did increase the number of AEs[10]. Thus, the combination of ribavirin and SOF/LDV is not approved in Japan for the treatment of chronic HCV infection, including in cirrhotic or treatment-experienced patients. Patients were divided into younger (< 75 years) and elderly (⩾ 75 years) groups, and clinical data were analyzed by group. This study was approved by the Research Ethics Committee of the University of Miyazaki.

Laboratory and virological assessments

Laboratory tests were performed at baseline, at weeks 4, 8, and 12 during therapy, and at 4, 8, and 12 wk after therapy. HCV RNA was measured using the COBAS TaqMan HCV test (Roche Diagnostics, Tokyo, Japan). The dynamic range was 1.2-7.8 log IU/mL. HCV RNA levels were measured at weeks 4, 8, and 12 during therapy, and at weeks 4, 8, and 12 after therapy. Liver cirrhosis was diagnosed clinically based on laboratory tests and imaging findings, including portosystemic shunt, splenomegaly, or esophageal/gastric varices. The fibrosis-4 index (Fib-4) was calculated before the initiation of SOF/LFV therapy. NS5A resistance-associated variants (RAVs) (Y93C/H/N/S or L31I/F/M/V) of HCV were tested by direct sequencing in some patients. In this study, virological responses were categorized as follows: Undetectable HCV RNA at 4 wk after the initiation of therapy was defined as rapid virological response (RVR), and that at 12 wk after the end of the therapy was defined as sustained virological response (SVR12). Relapse was defined as undetectable HCV RNA levels by the end of therapy and detectable levels during the follow-up period.

Statistical analysis

Statistical analyses were performed with SPSS software (IBM SPSS Statistics for Windows, version 20.0). Baseline continuous data are expressed as median, and categorical data are expressed as number and percentage. The effectiveness of SOF/LDV therapy was evaluated using intention-to-treat analysis. Univariate analyses were performed using the χ^2, Fisher's exact, or Mann-Whitney *U* tests. *P* values < 0.05 were considered statistically significant in all analyses.

RESULTS

Patient characteristics

Patient characteristics are shown in Table 1. The median age was 69 years (range, 29-88 years), and 79 (32%) patients were aged ⩾ 75 years (elderly group). Of the 246 patients, 103 (42%) were male. Fifty-one patients (21%) had cirrhosis, and all were Child-Pugh class A. Sixteen patients (7%) were previously treated for HCC. Fifty-two patients (21%) previously received interferon-based therapy. Of the 75 patients who were tested for HCV NS5A-RAVs before therapy, 22 (29%) were positive at baseline. Of these, only five had both NS5A Y93 and L31. Before therapy, the median HCV viral load was 6.1 log IU/mL (range 1.6-7.3 log IU/mL). Baseline platelet count and glomerular filtration rate were lower and FIB4 was higher in the elderly.

Effectiveness

The overall RVR rate was 86.9%. All patients had undetectable HCV RNA at 8 wk of therapy, and none exhibited viral breakthrough during treatment. The SVR12 rates were 99.2%, 99.4%, and 98.7% in the overall population and in patients aged < 75 and ⩾ 75 years, respectively. Table 2 shows the SVR12 rates according to various clinical and demographic factors. There was no difference between the two groups in any parameter. Two patients experienced virological relapse, one after 4 wk (elderly patient) and the other after 8 weeks (younger patient), and one of these had an NS5A RAV (L31M) at baseline.

Safety and adverse events

The safety profile for SOF/LDV is shown in Table 3. Common AEs during therapy were headache, pruritus, constipation, and insomnia. All were found in fewer than 10% of patients, at similar rates in the elderly and younger groups. Serious AEs, including hematological and laboratory abnormalities, were rare. None of the patients had decreased hemoglobin levels or platelet counts, and none had elevated total bilirubin levels over 3.0 mg/dL, alanine aminotransferase levels over five times the upper limit of normal, or creatinine levels over 1.5 times baseline values. Two patients (0.8%) discontinued therapy prematurely, one due to cerebral hemorrhage (pontine hemorrhage) at 7 wk after initiation of therapy, and one due to a skin eruption after 10 wk. The former was a 62-year-old man, while the latter was a 72-year-old woman. Both patients were treatment naïve, and eventually achieved SVR12.

DISCUSSION

Recently, a number of oral direct-acting antivirals (DAAs)

Table 1 Baseline characteristics

Characteristics	Total (n = 246)	< 75 yr (n = 167)	⩾ 75 yr (n = 79)	P value
Sex (male)	103 (42)	65 (39)	37 (47)	0.239
Age (yr)	69 (29-88)	65 (29-74)	78 (75-88)	< 0.001
Body weight (kg)	53 (35-91)	53 (38-91)	53 (35-78)	0.527
Cirrhosis	51 (21)	30 (18)	21 (26)	0.120
HCV RNA (log_{10}IU/mL)	6.1 (1.6-7.3)	6.1 (1.6-7.3)	6.1 (4.0-6.8)	0.337
Hemoglobin (g/dL)	13.6 (9.0-16.8)	13.6 (9.5-16.8)	13.3 (9.0-15.9)	0.163
Platelets (× 10^9/L)	156 (26-340)	167 (26-340)	132 (57-278)	0.001
Aspartate aminotransaminase (U/L)	42 (17-191)	40 (17-191)	45 (20-155)	0.140
Alanine aminotransaminase (U/L)	38 (11-319)	38 (12-319)	37 (11-167)	0.341
eGFR (mL/min per 1.73 m^2)	72 (36-132)	76 (38-132)	63 (36-98)	< 0.001
α-fetoprotein (ng/mL)	4 (1-382)	4 (1-382)	4 (1-74)	0.525
Fib-4 index	3.3 (0.5-23.2)	2.5 (0.5-23.2)	4.4 (1.5-10.7)	< 0.001
NS5A RAVs				
Y93	22 (29)	10 (21)	12 (43)	0.146
L31	6 (8)	3 (6)	3 (11)	0.798
Y93/L31	5 (7)	4 (9)	1 (4)	0.645
Treatment experienced	52 (21)	41 (25)	11 (14)	0.064
Previous HCC treatment	16 (7)	11 (7)	5 (6)	0.841

Data are expressed as n (%) or median (range). eGFR: Estimated glomerular filtration rate; RAVs: Resistance-associated variants; HCC: Hepatocellular carcinoma.

Table 2 Sustained virological response 12 rates according to clinical and demographical factors

Parameters	n	SVR 12 (%)	P value
Sex			0.6272
Male	103	100.0	
Female	143	98.6	
Age (yr)			0.8287
< 75	167	99.4	
⩾ 75	79	98.7	
HCV RNA (log10IU/mL)			0.7076
< 6.0	93	100.0	
⩾ 6.0	153	98.7	
Liver fibrosis			0.8811
No cirrhosis	195	99.5	
Cirrhosis	51	98.0	
Fib-4 index			0.4634
< 3.25	125	100.0	
⩾ 3.25	121	98.3	
Prior treatment			0.8931
Treatment naïve	194	99.0	
Treatment experienced	52	100.0	
Previous HCC treatment			0.2868
No	230	99.6	
Yes	16	93.8	
NS5A RAVs			0.5471
None	48	97.9	
Y93	22	100.0	
L31	6	83.3	
Y93/L31	5	100.0	

RAVs: Resistance-associated variants; HCC: Hepatocellular carcinoma; SVR: Sustained virological response.

Table 3 Safety profile

	Total (n = 246)	< 75 yr (n = 167)	⩾ 75 yr (n = 79)
Common adverse effects			
Headache	6 (2.4)	4 (2.4)	2 (2.5)
Pruritus	2 (0.8)	0	2 (2.5)
Constipation	2 (0.8)	2 (1.2)	0
Stomatitis	2 (0.8)	2 (1.2)	0
Skin eruption	1 (0.4)	1 (0.6)	0
Chill	1 (0.4)	1 (0.6)	0
Nausea	1 (0.4)	1 (0.6)	0
Fever	1 (0.4)	1 (0.6)	0
Insomnia	1 (0.4)	1 (0.6)	0
Hematological abnormalities			
Hemoglobin < 10.0 g/dL	0	0	0
Platelet count < 50 × 10^9/L	0	0	0
Laboratory abnormalities			
Total bilirubin > 3.0 mg/dL	0	0	0
Alanine aminotransferase > 5 × ULN	0	0	0
Serum creatinine > 1.5 × baseline	0	0	0
Death	0	0	0
Discontinuation due to adverse effects	2 (0.8)	2 (1.2)	0
Cerebral hemorrhage	1 (0.4)	1 (0.6)	0
Skin eruption	1 (0.4)	1 (0.6)	0

Data are expressed as n (%).

for HCV treatment were introduced worldwide, and have been reported to be more effective and safer compared with IFN-based therapies. In 2015, the combination of the NS5B polymerase inhibitor SOF and the NS5A inhibitor LDV was approved in Japan[10]. This regimen have demonstrated high efficacy with an improved safety profile and shorter therapy duration than interferon-based therapies, however, patients aged ⩾ 75 years were excluded from this clinical trials[10]. Moreover, the majority of Japanese patients with hepatitis C are elderly, and in particular, those aged ⩾ 75 years account for more than 50% of this population[5]. In our study, patients aged ⩾ 75 years showed a high SVR rate (98.7%) and none discontinued treatment due to AEs. Moreover, both the SVR rate and rate of discontinuation secondary to AEs were nearly equal in elderly (⩾ 75 years) and younger (< 75 years) patients. Although real-world cohort studies demonstrating the effectiveness of several SOF-containing regimens in elderly patients

have been published worldwide[14-16], to the best of our knowledge, this is the first real-world study focusing on a high SVR rate and low discontinuation rate due to AEs in Japanese HCV genotype 1 patients aged ⩾ 75 years following SOF/LDV therapy.

Elderly patients in the present study were more likely to have advanced liver fibrosis than younger patients because of their lower platelet counts and higher Fib-4 index. This is consistent with a previous report showing that the prevalence of advanced fibrosis was higher in the elderly than in a younger population[17]. Only 32% of the HCV patients in our sample were over 75 years old, while Karino[5] found that over 50% of people with HCV in Japan are age 75 years or older, as mentioned above. Elderly patients accounts for the majority of those with advanced cirrhosis (Child-Pugh class B or C), and patients with this condition were excluded from the present analysis. It is suggested that this is the reason for the relatively low proportion of elderly patients (⩾ 75 years) compared with younger patients (< 75 years) in our study. Although advanced fibrosis was found to lower the SVR rate achieved by interferon-based therapy in patients with HCV genotype 1[18], SOF/LDV therapy resulted in similarly high SVR rates in cirrhotic and non-cirrhotic patients, both in a clinical trial[10] and in the real world[19-21]. Likewise, in our study the SVR rate was high irrespective of liver status.

Two of 246 patients in our study experienced virological relapse, one of whom had an NS5A RAV (L31M) at baseline. Although pre-existing NS5A and NS5B RAVs for HCV genotype 1b were shown to have a minimal influence on SVR rates following SOF/LDV therapy[22,23], Ogawa *et al*[24] reported that cirrhotic patients with pre-existing NS5A RAVs had significantly lower SVR12 rates than those without these RAVs at baseline. In the present study, one of the two relapsed patients had an NS5A RAV (L31M) and liver cirrhosis, which may have prevented the achievement of SVR12. However, the other had no NS5A RAVs or cirrhosis at baseline, so there were no common factors that were obviously associated with therapy failure.

Our study has several limitations. First, it used a retrospective design. Second, NS5A RAVs could not be tested in all patients and few patients failed to achieve SVR12, therefore we could not correlate NS5A RAVs with therapy failure. Further research including a large number of patients is necessary.

In conclusion, SOF/LDV therapy resulted in similarly high virological response and good tolerance in elderly and younger patients, and may therefore be effective and safe in patients aged ⩾ 75 years.

ARTICLE HIGHLIGHTS

Research background

The majority of Japanese patients with hepatitis C are elderly, however, elderly patients (⩾ 75 years) treated with interferon (IFN)-based therapies have poor sustained virological response (SVR) rates and high discontinuation rates due to AEs. As a result, it is critical that new anti-viral therapies be developed for elderly patients. The combination of sofosbuvir (SOF) and ledipasvir (LDV) was approved in Japan, and though this regimen has demonstrated high efficacy with an improved safety profile and shorter therapy duration than IFN-based therapies, there are few real-world studies of Japanese patients aged ⩾ 75 years.

Research motivation

Evaluating the efficacy and safety of SOF and LDV in elderly patients with hepatitis C genotype 1 will help clinicians assess whether they can treat these patients similarly to younger patients in the real-world.

Research objectives

To evaluate the efficacy and safety of SOF and LDV in Japanese elderly patients with hepatitis C genotype 1.

Research methods

Demographic, clinical, virological, and AE-related data obtained during and after SOF/LDV therapy were retrospectively collected from medical records.

Research results

The SVR rates at 12 wk after treatment were 99.2%, 99.4%, and 98.7% in the overall population and in patients aged < 75 and ⩾ 75 years, respectively. Common AEs occurred in fewer than 10% of patients, and their incidence was not significantly different between the younger and elderly groups.

Research conclusions

The present study demonstrated that patients aged ⩾ 75 years had a similar virological response and tolerance to SOF/LDV therapy compared with patients aged < 75 years in a real-world cohort. Therefore, SOF/LDV therapy might be effective and safe in elderly patients.

Research perspectives

Further prospective studies with large sample sizes are necessary.

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ORIGINAL ARTICLE

Retrospective Study

Women receive more inpatient resections and ablations for hepatocellular carcinoma than men

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Abstract

AIM

To evaluate disparities in the treatment of hepatocellular carcinoma (HCC) based on gender.

METHODS

A retrospective database analysis using the Nationwide Inpatient Sample (NIS) was performed between 2010 and 2013. Adult patients with a primary diagnosis of hepatocellular carcinoma determined by International Classification of Disease 9 (ICD-9) codes were included. Univariate analysis and multivariate logistic regressions were performed to analyze differences in treatment, mortality, features of decompensation, and metastatic disease based on the patient's gender.

RESULTS

The analysis included 62582 patients with 45908 men

and 16674 women. Women were less likely to present with decompensated liver disease (OR = 0.84, P < 0.001) and had less risk of inpatient mortality when compared to men (OR = 0.75, P < 0.001). Women were more likely to receive inpatient resection (OR = 1.31, P < 0.001) or an ablation (OR = 1.22, P = 0.028) than men. There was no significant difference between men and women in regard to liver transplantation and transcatheter arterial chemoembolization (TACE).

CONCLUSION

Gender impacts treatment for hepatocellular carcinoma. Women are more likely to undergo an ablation or resection then men. Gender disparities in transplantation have resolved.

Key words: Hepatocellular carcinoma; Gender disparities; Liver transplantation; Liver resection; Ablation

Core tip: Previous studies have evaluated treatment disparities in the treatment of hepatocellular carcinoma (HCC) based on gender. Despite recent emphasis to ensure equal care for all patients this study continues to show disparities in the treatment of HCC, specifically in resection and ablation. Gender disparities in the treatment of HCC with transplantation have resolved.

Sobotka L, Hinton A, Conteh L. Women receive more inpatient resections and ablations for hepatocellular carcinoma than men. *World J Hepatol* 2017; 9(36): 1346-1351 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i36/1346.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i36.1346

INTRODUCTION

The incidence of hepatocellular carcinoma (HCC) in the United States is increasing. In 2016, it is estimated that more than 35000 people in the United States will be diagnosed[1]. The diagnosis has tripled since the 1980s. Men are three times as likely to be diagnosed with HCC as women[2]. Once diagnosed with HCC, survival rates are dependent on the stage with a 5 year survival of approximately 30.5 and metastatic HCC survival of 3.1[2].

There has been an emphasis on evaluating gender disparities in healthcare; HCC is not an exception. Gender disparities in the treatment for HCC have been noted in the past, specifically in transplantation. Studies reveal that men were more likely to receive a liver transplantation during pre-Model for End Stage Liver Disease (MELD) organ allotment, while women were more likely to die while waiting for organ transplantation[3]. Other studies have concluded that women were more likely to receive resection for earlier stage disease[4].

The aim of this study is to use the Nationwide Inpatient Sample (NIS) to determine if gender disparities still exist in the inpatient treatment for HCC.

We hypothesize that gender disparities continue to exist and seek to identify potential factors associated with this disparity.

MATERIALS AND METHODS

Data source

Data was obtained from the NIS, which is a component of the Healthcare Cost and Utilization Project (HCUP). This is the largest publically available database in the United States specifically designed to analyze data regarding hospital inpatient stays. Data is collected from over 1000 hospitals and represents more than 35 million discharges annually. The database contains clinical and research use information regarding primary and secondary diagnoses and procedures, patient demographics, length of stay, severity, and comorbidity measures[5].

Data was obtained between 2010 and 2013 and included patients 18 and older with a primary diagnosis of HCC using ICD-9 code of 155.0. This ICD-9 code has been utilized in other peer reviewed manuscripts[6].

Demographic information collected included age, gender, and race. Other evaluated information included risk factors of HCC, comorbidities, metastasis, and features of liver decompensation.

Degree of decompensation was characterized by the number of complications, including ascites, coagulopathy, esophageal varices, portal hypertension, encephalopathy, edema, and hepatorenal syndrome. Metastases were categorized as none, single, and greater than two sites. Comorbidities were evaluated using the Elixhauser Comorbidity Score which was modified to exclude liver disease and metastatic cancer[7].

Treatment was identified using ICD-9 codes and included transplantation, resection, ablation, and transarterial chemoemolization (TACE). If a patient did not receive treatment, the patient was listed as "noninvasive therapy." If a patient had multiple admissions in which treatment was performed, they were assigned to treatment group by their most invasive treatment.

The Ohio State University Data and Specimen Policy and Human Subjects Research Policy does not require Institutional Review Board approval for population-based public data sets. Per 45 Code of Federal Regulations (CFR 46.101), research using certain publicly available data sets does not involve "human subjects".

Statistical analysis

Associations between gender and factors of interest were evaluated using χ^2 tests. Multivariate regression models were fit for the presence of metastatic HCC, liver decompensation, mortality, and treatment. Terms included in each model were determined through backwards selection where hepatitis C, hepatitis B, alcohol, NASH, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune liver disease, features of liver

Table 1 Demographic and clinical parameters in patients with hepatocellular carcinoma grouped by gender between 2010 and 2013

	Male (*n* = 45908)		Female (*n* = 16674)		*P* value
	n	%	*n*	%	
Age (yr)					< 0.001
⩽ 64	28784	62.70	7847	47.06	
65-79	13683	29.81	6226	37.34	
⩾ 80	3441	7.50	2602	15.60	
Race					0.865
Caucasian	23845	51.94	8583	51.47	
African-American	7172	15.62	2554	15.32	
Hispanic	6572	14.32	2416	14.49	
Asian	3660	7.97	1316	7.89	
Others/unknown	4658	10.15	1806	10.83	
Primary payer					< 0.001
Medicare	18592	40.50	8803	52.79	
Medicaid	9198	20.04	2426	14.55	
Private insurance	12757	27.79	4139	24.82	
Self-pay	2771	6.04	695	4.17	
No charges	319	0.70	76	0.46	
Unknown/other	2270	4.95	535	3.21	
Geographic region					0.006
Northeast	10910	23.77	3643	21.85	
Midwest	7929	17.27	3311	19.86	
South	16808	36.61	5961	35.75	
West	10261	22.35	3759	22.54	
Hepatitis C	8449	18.40	2359	14.15	< 0.001
Hepatitis B	2839	6.18	580	3.48	< 0.001
Alcohol	9102	19.83	923	5.53	< 0.001
NASH	15935	34.71	6044	36.24	0.126
Primary sclerosing cholangitis	394	0.86	188	1.13	0.171
Primary biliary cirrhosis	51	0.11	123	0.74	< 0.001
Autoimmune	50	0.11	136	0.81	< 0.001
Other	17124	37.30	8542	51.23	< 0.001
Liver decompensation Features					< 0.001
Zero	24826	54.08	10538	63.20	
One	13348	29.08	4308	25.84	
Two	6126	13.34	1539	9.23	
Three or greater	1608	3.50	289	1.73	
Metastasis					0.627
None	38219	83.25	13992	83.92	
Single site	5954	12.97	2052	12.30	
Two or more sites	1735	3.78	630	3.78	
Elixhauser comorbidity Score					
< 3	22662	49.36	7982	47.87	0.141
⩾ 3	23246	50.64	8692	52.13	
Treatment options					
Transplant	1553	3.38	492	2.95	
Resection	4945	10.77	2551	15.30	
Ablation	2702	5.89	1103	6.62	
TACE	3701	8.06	1241	7.44	
Noninvasive treatment	33007	71.90	11288	67.70	

NASH: Non-alcoholic steatohepatitis; TACE: Transcatheter arterial chemoembolization.

decompensation, metastasis, treatment, and Elixhauser comorbidity were all eligible for inclusion, where appropriate. Analyses were performed using weighted data employing appropriate survey procedures to produce national estimates. Data was analyzed using SAS software (version 9.4 SAS Institute Inc. Cary, NC, United States).

RESULTS

Demographics

There were 62582 patients with a primary diagnosis of HCC included in the study (Table 1). The majority (45908; 73) of patients was male and Caucasian (52). The major identifiable insurance payer was Medicare (44).

Liver severity, evidence of metastasis of HCC and inpatient mortality

Women were more likely to present without evidence of decompensated disease than men ($P < 0.001$). There was no difference between genders in patients with metastatic disease. Women had a lower rate of inpatient mortality ($P < 0.001$) (Table 1).

On multivariate analysis, there was no significant

Table 2 Multivariate logistic regression comparing outcomes of hepatocellular carcinoma by gender

Outcome	Gender	OR	95%CI	*P* value
Metastatic hepatocellular carcinoma[1]	Male	1.00	0.84, 1.05	0.303
	Female	0.94		
Liver decompensation[2]	Male	1.00	0.77, 0.92	< 0.001
	Female	0.84		
Inpatient mortality[3]	Male	1.00	0.65, 0.87	< 0.001
	Female	0.75		

[1]Model is adjusted for age, primary payer, hepatitis C, alcohol, non-alcoholic steatohepatitis (NASH), liver decompensation features, and Elixhauser comorbidity score; [2]Model is adjusted for age, race, primary payer, geographic region, hepatitis C, alcohol, NASH, primary biliary cirrhosis, metastasis, and Elixhauser comorbidity score; [3]Model is adjusted for age, race, primary payer, hepatitis C, hepatitis B, alcohol, NASH, liver decompensation features, metastasis, and treatment.

Table 3 Multinomial logistic regression to evaluate gender disparities in treatment for hepatocellular carcinoma[1,2]

Treatment	Gender	OR	95%CI	*P* value
Liver transplant	Male	1.00	0.95, 1.50	0.132
	Female	1.19		
Resection	Male	1.00	1.15, 1.48	< 0.001
	Female	1.31		
Ablation	Male	1.00	1.02, 1.45	0.028
	Female	1.22		
TACE	Male	1.00	0.84, 1.16	0.841
	Female	0.98		

[1]Noninvasive treatment is treated as the reference category; [2]Model adjusts for age, race, primary payer, hepatitis C, hepatitis B, alcohol, NASH, primary sclerosing cholangitis, primary biliary cirrhosis, liver decompensation features, metastasis, and Elixhauser comorbidity score. NASH: Non-alcoholic steatohepatitis; TACE: Transcatheter arterial chemoembolization.

difference between rates of metastatic HCC in men *vs* women. Women were less likely to present with evidence of decompensated disease (OR = 0.84, $P < 0.001$). Women had a significantly smaller risk of inpatient mortality (OR = 0.75, $P < 0.001$) (Table 2).

Inpatient treatment of HCC

Women were more likely to receive a resection with 15 of women receiving this treatment compared to 11 of men. The gender disparity rate was to a lesser extent for the other treatments. However, 71 of the patients included in this study are listed as "noninvasive treatment" which includes patients that did not undergo transplant, resection, ablation, or TACE (Table 1).

On multivariate analysis, women were more like to have a resection (OR = 1.31, $P < 0.001$) and an ablation (OR = 1.22, $P = 0.028$). There were no significant differences between the rates of transplantation or TACE (Table 3).

DISCUSSION

This study shows gender differences for the inpatient management of HCC. Women are still more likely to undergo resection which is consistent with prior publications. This study also determined that women are more likely to undergo ablation. Women may be more likely to undergo these procedures because of functional status, compensated disease, and increased likelihood of undergoing screening exams that allow them to be diagnosed earlier. Despite advances in treatment of HCC, females are more likely to receive curative treatment with resection and ablation. It is important to recognize this difference and find ways to reduce it given that ablations and resections are associated with lower costs and decreased 30-d mortality.

Multiple factors predispose a patient to develop HCC, including cirrhosis of the liver, hepatitis B and C[8]. Screening for HCC consists of a liver ultrasound and serum alpha fetoprotein (AFP) every 6 mo. Once an abnormal screening exam is found, patients will undergo triple phase CT or MRI of the liver. If a nodule has imaging characteristics that are stereotypical for HCC, a diagnosis of HCC can be made and biopsy is not necessary. If the nodule is smaller, a biopsy can be performed to confirm diagnosis[9]. Once diagnosed with HCC, staging and treatment are determined. The Barcelona Liver Clinic Staging Classifications is widely used to determine treatment based on the size of the lesion. Early stage disease is defined as 1 to 3 nodules less than 3 cm; therefore, treatment with resection, liver transplantation, ablation, or TACE are more viable options and could be considered curative[10].

Women continue to receive certain curative treatments for HCC more frequently than men and there are multiple factors that likely contribute to this. Studies show that patients are more likely to undergo curative treatment if they present with compensated disease and good functional status. This study and previous studies have shown that women are more likely to present with

compensated liver disease than men. Previous studies have shown slower progression of disease making women more likely to receive curative treatment. Multiple theories support these findings including studies that show estrogen can prevent stellate cell activation which plays a major factor in developing underlying liver fibrinogenesis and women are less likely to have complications such as portal vein thrombosis and renal dysfunction that may prohibit them from undergoing curative treatment[11].

Patients who undergo regular screening for HCC are also more likely to be diagnosed with early stage disease *vs* metastatic disease and would be a better candidate for curative treatment. Studies have shown that women are more likely to follow stricter screening protocols than men which may allow earlier diagnosis of HCC when it is still at a size that is amendable to treatment with ablation or resection[12].

It is important to understand why this is relevant in daily practice. This difference in treatment can have a profound effect on healthcare costs, mortality, and rates of metastatic disease, which is crucial to recognize in a time of rapid increase in healthcare expenditures and increasing mortality rates in patients with HCC.

Women are presenting with more compensated disease and tumor size that is amendable to resection and ablation and are able to receive these interventions in a timelier manner compared to liver transplant. This could theoretically decrease the chances of developing metastatic disease, though this is not reflected in the data from this study.

Ablation and resection are curative treatments like a liver transplant; however, they have less of a financial burden on the medical system. United Network for Organ Sharing (UNOS) estimated that the average cost for a liver transplant in 2011 was $577100 with all other forms of treatment being less expensive[13]. It is important to recognize the factors that make women more likely to undergo these procedures and apply these across both genders in order to facilitate a quality driven and fiscally responsible healthcare system.

Mortality must also be considered a crucial factor when analyzing the importance of women receiving more ablation and resections than men. This study shows that women have a smaller risk of inpatient mortality; this may be partially due to women undergoing these less invasive procedures more frequently than men. The mortality rate is around 4[14] for liver resection and 1.5 for ablation[15]. For patients undergoing liver transplant, the mortality rate is greater and is estimated to be 7 to 17 30-d mortality rate[16]. Ablation and resection can also be curative; however, they have a decreased risk of 30-d mortality compared to transplant, and therefore should be considered an ideal for of treatment for both men and women.

This study does have limitations: the most important being the use of administrative data and the accuracy of ICD-9 CM coding. These codes could not be verified by medical chart given privacy issues and are susceptible to error. This study was completed using data obtained from an inpatient database and therefore does not include patients that may have received procedures as an outpatient. Size of tumor effects treatment, however the effect of tumor size on treatment could not be determined with the use of the NIS. Given this study uses administrative data, we are unable to determine MELD score or Childs Pugh Score and therefore used factors of liver decompensated to determine disease severity.

In conclusion, this study shows that a gender difference in the treatment of HCC continues to exist, specifically with resection and ablation. It is important to recognize this disparity and make an effort to reduce this given that interventions are associated with decreased financial burden and lower 30-d mortality rate. It is unclear why this disparity continues to exist, and further research should be completed to determine the cause and ways to reduce this difference between genders.

ARTICLE HIGHLIGHTS

Research background

Gender disparities have been noted in the treatment of hepatocellular carcinoma (HCC), specifically with liver transplantation.

Research motivation

There has been an emphasis on evaluating gender disparities in healthcare; HCC is not an exception. Gender disparities in the treatment for HCC have been noted in the past, specifically in transplantation. Studies reveal that men were more likely to receive a liver transplantation during pre-model for end stage liver disease (MELD) organ allotment, while women were more likely to die while waiting for organ transplantation. Other studies have concluded that women were more likely to receive resection for earlier stage disease.

Research objectives

The aim of this study is to determine if disparities continue to exist despite an emphasis to reduce disparities in healthcare.

Research methods

A retrospective database analysis utilizing the NIS was performed.

Research results

The authors determined that women are more likely to undergo an ablation or resection then men. Disparities in liver transplantation have resolved. Further research should be completed to determine ways to reduce gender disparities in hepatocellular carcinoma given the effect this has on patient mortality and healthcare cost.

Research conclusions

This study shows that a gender difference in the treatment of HCC continues to exist, specifically with resection and ablation. It is important to recognize this disparity and make an effort to reduce this given that interventions are associated with decreased financial burden and lower 30-d mortality rate.

Research perspectives

It is unclear why the previous disparity continues to exist, and further research should be completed to determine the cause and ways to reduce this difference between genders.

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ORIGINAL ARTICLE

Retrospective Study

Impact of sustained virologic response on chronic kidney disease progression in hepatitis C

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Author contributions: Aby ES, Dong TS, Kawamoto J, Pisegna JR and Benhammou JN were involved in study concept and design; Aby ES and Dong TS were involved in data acquisition; Aby ES, Dong TS and Benhammou JN were involved in analysis and interpretation of data; Aby ES drafted the manuscript; Dong TS, Pisegna JR and Benhammou JN were involved in critical revision of the manuscript for important intellectual content; Dong TS performed the statistical analysis; Pisegna JR provided administrative, technical and material support as well as study supervision.

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Abstract

AIM

To determine how sustained virological response at 12 wk (SVR12) with direct acting antivirals (DAAs) for the treatment of hepatitis C virus (HCV) infection affects chronic kidney disease (CKD) progression.

METHODS

A retrospective analysis was performed in patients aged ⩾ 18 years treated for HCV with DAAs at the VA Greater Los Angeles Healthcare System from

2014-2016. The treatment group was compared to patients with HCV from 2011-2013 who did not undergo HCV treatment, prior to the introduction of DAAs; the control group was matched to the study group in terms of age, gender, and ethnicity. Analysis of variance and co-variance was performed to compare means between SVR12 subgroups adjusting for co-variates.

RESULTS

Five hundred and twenty-three patients were evaluated. When comparing the rate of change in estimated glomerular filtration rate (eGFR) one-year after HCV treatment to one-year before treatment, patients who achieved SVR12 had a decline in GFR of 3.1 mL/min ± 0.75 mL/min per 1.73 m^2 compared to a decline in eGFR of 11.0 mL/min ± 2.81 mL/min per 1.73 m^2 in patients who did not achieve SVR12 (P = 0.002). There were no significant clinical differences between patients who achieved SVR12 compared to those who did not in terms of cirrhosis, treatment course, treatment experience, CKD stage prior to treatment, diuretic use or other co-morbidities. The decline in eGFR in those with untreated HCV over 2 years was 2.8 mL/min ± 1.0 mL/min per 1.73 m^2, which was not significantly different from the eGFR decline noted in HCV-treated patients who achieved SVR12 (P = 0.43).

CONCLUSION

Patients who achieve SVR12 have a lesser decline in renal function, but viral eradication in itself may not be associated improvement in renal disease progression.

Key words: Hepatitis C; Direct-acting antivirals; Chronic kidney disease; End stage renal disease; Sustained virological response

Core tip: In hepatitis C patients treated with direct acting antivirals, there is a lesser decline in renal function in those who are treated and achieved sustained virological response at 12 wk (SVR12) compared to those who do not achieve SVR12. However, the decline in renal function is no different between those who achieve SVR12 and those who are never treated. This suggests that viral eradication may not be associated improvement in the progression of renal disease and other factors, such as cryoglobulinemia, may be implicated in renal disease progression.

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INTRODUCTION

Hepatitis C virus (HCV) is a significant public health issue that affects around 3 million individuals in the United States[1]. The prevalence of chronic HCV infection in veterans affairs (VA) healthcare users is more than 2-fold higher than the general United States population, thus being the nation's largest provider for HCV care[2,3].

The consequences of HCV infection extend beyond the liver, including renal complications such as membranoproliferative glomerulonephritis (MPGN) in the setting of cryoglobulinemia[4]. Patients with HCV were found to have a five-fold increase in the odds of developing MPGN compared with individuals who were not infected[5]. Chronic HCV infection has also been associated with reductions in glomerular filtration rate (GFR) < 60 mL/min per 1.73 m^2, development of end-stage renal disease (ESRD), and a rapid decline in renal function[4,6-9]. Interestingly, the duration of chronic HCV infection influences the risk of developing chronic kidney disease (CKD)[10]. Previous systematic reviews suggest a relationship between HCV infection and higher incidence of low estimated GFR (eGFR)[11]. In a meta-analysis of nearly 3 million individuals, chronic HCV infection predicted a 51% increase in the risk of proteinuria and a 43% increase in the incidence of CKD[11]. CKD is an important public health problem as it increases the likelihood of adverse outcomes and is associated with high healthcare costs[12].

Given that HCV infection is associated with CKD progression, the aim of our study was to determine if the achievement of sustained virological response at 12 wk (SVR12) with interferon-free, direct acting antivirals (DAAs) impacts the progression of CKD. We hypothesize that viral eradication would result in a reduction in CKD progression. No previous study has rigorously investigated whether eradication of HCV infection with newer DAA therapies is associated with improved renal function.

MATERIALS AND METHODS

Data source and study population: The VA Greater Los Angeles Healthcare System (VAGLAHS) institutional review board approved this study. Data were abstracted using the Corporate Data Warehouse, a national repository of patient data, for all patients evaluated at the VAGLAHS. A retrospective medical records review was performed by reviewing those patients over 18 years of age who initiated hepatitis C treatment with interferon-free DAAs from January 1st, 2014 to June 1st, 2016. The control group consisted of patients over 18 years of age who did not undergo hepatitis C treatment from January 1st, 2011 to January 1st, 2013, prior to the introduction of DAAs; the control group was matched to the study group in terms of age, gender and ethnicity.

Baseline patient characteristics

Demographic data, including age, gender, body mass index (BMI) and ethnicity, were obtained at the initial visit. Baseline laboratory data were collected at the time of initial visit. Serum creatinine and estimated

GFR were collected yearly for two consecutive years before and one year after treatment. Patients were excluded if there was incomplete kidney function data one year after treatment. Patients were also excluded if they were lost to follow-up or died within 1 year of treatment. The diagnoses of comorbidities were based on International Classification of Disease, Ninth Revision and/or Tenth Revision, Clinical Modification (ICD-9 CM/ICD-10 CM) and use of anti-hypertensive or diabetes medications. The ICD-9/ICD-10 codes that were used were 250.00-250.93/E08-E13 for diabetes mellitus and 401.0, 401.1 and 401.9/I10 for essential hypertension. Cirrhosis and diuretic use were determined through chart review of hepatology provider notes. Patients receiving hemodialysis therapy were excluded. HCV patients were identified by ICD-9/ICD-10 coding, 070.0-0.70.1/B18.2 and B19.2. The primary outcome of our study was SVR12, which was defined as an undetectable HCV RNA (< 15 IU/mL) 8, 12 wk or beyond the conclusion of treatment[13].

Statistical analysis

Patient characteristics were measured by continuous and categorical variables. The baseline stage of kidney disease was measured with the GFR at the time of treatment as defined by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative[14]. The mean values of baseline characteristic were analyzed using student's *t*-test. Proportions were compared using χ^2 test. Medians were compared using the Wilcoxon rank-sum test. The mean GFR of the control group and the treatment group was tested for a normal distribution by using a kernel density estimation. Mean GFR between groups were compared using analysis of variance. Analyzed covariates included gender, age by tertile, ethnicity, treatment experience, HCV genotype, treatment regimen, baseline kidney disease, diuretic use, and the presence of such comorbidities as obesity, hypertension, diabetes, heart failure (CHF), coronary artery disease (CAD), and peripheral artery disease (PAD). In addition, the change in eGFR from 1-year prior to DAA initiation was calculated and compared to the change in eGFR between DAA initiation and 1-year post-DAAs; a paired *t*-test was performed. A *P* value of < 0.05 was considered as significant. Data analysis was done using STATA® v14.2.

RESULTS

A total of 523 patients met inclusion criteria for the study. Baseline characteristics of the cohort are presented in Table 1. The majority of patients were white males with a mean age of 62.7 (SE ± 0.3) years. A total of 48.6% had cirrhosis and 22.4% were treatment-experienced. Thirty-two percent had diabetes, 68.5% had hypertension, 10.1% had CAD, 4.2% had CHF and 2.9% had been diagnosed with PAD. The most common genotype was genotype 1a (53.2%) followed by genotype 1b (28.1%). The most common HCV treatment regimen was a combination of ledipasvir with sofosbuvir followed by sofosbuvir plus ribavirin. The majority of patients were CKD stages 1 or 2 prior to HCV treatment.

Within the treated groups, there was a significant difference in age between patients who achieved SVR12 compared to those who did not, with the group who achieved SVR12 being slightly older (*P* = 0.02). There were no other significant clinical differences between patients who achieved SVR12 compared to those who did not in terms of gender, ethnicity, cirrhosis, treatment course, treatment experience, CKD stage prior to treatment, diuretic use or other co-morbidities.

The control group consisted of 439 patients who were not treated for HCV and followed from January 1st, 2011 to January 1st, 2013. These patients were not treated for HCV given that DAAs were not available at VAGALHS during that time period. Baseline characteristics of the study population and control groups are shown in Table 2. The control group was matched to the treatment group by age, gender, and ethnicity. The control group was not statistically different from the cohort of HCV treated patients in terms of age, gender, ethnicity, HCV genotype, diabetes, CAD, PAD, CKD stage prior to treatment, and diuretic use. The median MELD score (interquartile range) for the cirrhotic patients at baseline was 8.4 (7.49-9.72) in the treatment group compared to 7.7 (6.43-9.16) in the control group that did not undergo treatment; there were no significant differences in MELD score between groups (*P* = 0.19). There were significantly more patients with cirrhosis and obesity (BMI > 30 kg/m^2) in the cohort who underwent HCV treatment compared to the control group (*P* = 0.001, 0.005 respectively). The control group, however, had significantly more patients with hypertension and CHF compared to the cohort who underwent HCV treatment (*P* = 0.02, 0.001 respectively).

When comparing the rate of change in eGFR one-year after HCV treatment compared to one-year before treatment, patients who achieved SVR12 had a decline in GFR of 3.1 mL/min ± 0.75 mL/min per 1.73 m^2 compared to a decline in eGFR of 11.0 mL/min ± 2.81 mL/min per 1.73 m^2 in patients who did not achieve SVR12 (*P* = 0.002; Figure 1). In those who achieved SVR12, the change in eGFR 1-year prior to treatment was -6.2 mL/min ± 1.06 mL/min per 1.73 m^2 compared to -1.8 mL/min ± 0.75 mL/min per 1.73 m^2 in the year following DAA therapy; those who achieved SVR12 had a lesser decline in renal function following DAA treatment (*P* = 0.002). In those who were treated with DAAs but did not achieve SVR12, the change in eGFR 1-year prior to treatment was -5.4 mL/min ± 2.79 mL/min per 1.73 m^2 compared to -7.42 mL/min ± 2.2 mL/min per 1.73 m^2 in the year following DAA therapy (*P* = 0.62). In the control group, the decline in eGFR over two years was 2.8 mL/min ± 1.0 mL/min per 1.73 m^2. This decline in eGFR in untreated patients over two years was not significantly different from the eGFR decline noted in patients who achieved SVR12 after

Table 1 Baseline characteristics for patients undergoing treatment for hepatitis C virus at the West Los Angeles Veterans Administration

	All patients (*n* = 523)	SVR12 not achieved (*n* = 38)	SVR12 achieved (*n* = 485)	*P* value
Age (mean, yr) (SE)	62.7 (0.3)	60.5 (1.1)	63.0 (0.3)	0.02[a]
Gender (%)				
Male (*n* = 512)	97.9	94.7	97.9	0.81
Female (*n* = 11)	2.1	5.3	2.1	
Ethnicity (%)				
White (*n* = 278)	53.2	52.6	56.3	0.78
Black or African American (*n* = 174)	33.3	34.3	33.2	
American Indian or Alaska Native (*n* = 11)	2.1	2.6	2.1	
Asian (*n* = 4)	0.8	2.6	0.6	
Native Hawaiian or other pacific islander (*n* = 5)	1.0	0.0	1.0	
Unknown/declined to answer (*n* = 51)	9.8	7.9	9.9	
Cirrhosis (%)				
Non-cirrhotic (*n* = 269)	51.4	47.2	51.7	0.31
Cirrhosis (*n* = 254)	48.6	52.8	48.3	
Treatment experience (%)				
Treatment naive (*n* = 406)	77.6	73.7	77.9	0.54
Treatment experienced (*n* = 117)	22.4	26.3	22.1	
HCV genotype (%)				
HCV genotype 1a (*n* = 278)	53.2	50.7	53.3	0.44
HCV genotype 1b (*n* = 147)	28.1	22.2	28.6	
HCV genotype 2 (*n* = 48)	9.2	12.6	8.9	
HCV genotype 3 (*n* = 40)	7.6	17.1	6.9	
HCV genotype 4 (*n* = 6)	1.1	0.0	1.2	
HCV genotype 6 (*n* = 1)	0.2	0.0	0.2	
Combination (*n* = 3)	0.6	0.0	0.6	
Treatment (%)				
Dasabuvir, ombitasvir, paritaprevir and ritonavir (*n* = 104)	19.9	23.7	19.6	0.68
Ledipasvir and sofosbuvir (*n* = 200)	38.2	44.7	37.7	
Simeprevir (*n* = 55)	10.5	5.3	10.9	
Sofosbuvir + Ribavirin (*n* = 164)	31.4	26.3	31.8	
Obesity (%)				
BMI < 30 (*n* = 284)	54.3	63.5	53.6	0.25
Obese (*n* = 239)	45.7	36.5	46.4	
Hypertension (%)				
No hypertension (*n* = 177)	33.8	47.5	32.8	0.07
Hypertension (*n* = 346)	68.5	52.5	67.2	
Diabetes (%)				
No diabetes (*n* = 358)	31.5	73.5	68.1	0.47
Diabetes (*n* = 165)	30.9	26.5	31.9	
Congestive heart failure (%)				
No congestive heart failure (*n* = 501)	95.8	97.4	95.7	0.2
Congestive heart failure (*n* = 22)	4.2	2.6	4.3	
Coronary artery disease (%)				
No coronary artery disease (*n* = 469)	89.7	94.7	89.3	0.12
Coronary artery disease (*n* = 53)	10.1	2.6	10.7	
Peripheral arterial disease (%)				
No peripheral arterial disease (*n* = 508)	97.1	94.7	97.2	0.99
Peripheral arterial disease (*n* = 15)	2.9	5.3	2.7	
Baseline CKD before treatment (%)				
Stage 1 CKD (*n* = 263)	50.3	60.5	49.5	0.24
Stage 2 CKD (*n* = 218)	41.7	39.5	41.9	
Stage 3 CKD (*n* = 41)	7.8	0.0	8.5	
Stage 4 CKD (*n* = 1)	0.2	0.0	0.2	
Diuretic use (%)				
No diuretic use (*n* = 367)	70.2	71.1	70.1	0.9
Diuretic use (*n* = 156)	29.8	28.9	29.9	

[a]Significant *P*-value, $P < 0.05$. CKD: Chronic kidney disease; HCV: Hepatitis C virus; SVR12: Sustained virological response at 12 wk following therapy.

HCV treatment ($P = 0.43$).

Figure 2 demonstrates the rate of change in eGFR one-year after HCV treatment compared to one-year before treatment stratified by genotype. In patients with genotype 1a and 1b, there was less of a decline in eGFR between one-year before HCV treatment compared to one-year after treatment in patients who achieved SVR12 compared to those who did not ($P = 0.02$). There was no significant difference in eGFR decline between patients who achieved SVR12 and

Table 2 Baseline characteristics for patients undergoing treatment for hepatitis C virus at the West Los Angeles Veterans Administration compared to patients with hepatitis C virus who did not undergo treatment

	All patients (n = 523)	Control patients (n = 439)	P value
Age (mean, yr) (SE)	62.8 (0.3)	63.2 (0.3)	0.13
Gender (%)			
Male	97.9	98.1	0.75
Female	2.1	1.9	
Ethnicity (%)			
White	53.2	55.4	0.3
Black or African American	33.3	35.1	
American Indian or Alaska Native	2.1	2.5	
Asian	0.8	0.5	
Native Hawaiian or other pacific islander	1.0	0.9	
Unknown/declined to answer	9.8	5.7	
Cirrhosis (%)			
Non-cirrhotic	51.4	72.0	0.001[a]
Cirrhosis	48.6	28.0	
HCV genotype (%)			
HCV genotype 1a	53.2	55.9	0.31
HCV genotype 1b	28.1	22.8	
HCV genotype 2	9.2	11.8	
HCV genotype 3	7.6	6.7	
HCV genotype 4	1.1	1.7	
HCV genotype 6	0.2	0.0	
Obesity (%)			
BMI < 30	54.3	63.3	0.005[a]
Obese	45.7	36.7	
Hypertension (%)			
No hypertension	33.8	26.7	0.02[a]
Hypertension	68.5	73.3	
Diabetes (%)			
No diabetes	68.5	64.0	0.15
Diabetes	31.5	36.0	
Congestive heart failure (%)			
No congestive heart failure	95.8	90.4	0.001[a]
Congestive heart failure	4.2	9.6	
Coronary artery disease (%)			
No coronary artery disease	89.7	88.4	0.46
Coronary artery disease	10.1	11.6	
Peripheral arterial disease (%)			
No peripheral arterial disease	97.1	95.2	0.09
Peripheral arterial disease	2.9	4.8	
Baseline CKD before treatment (%)			
Stage 1 CKD	50.3	47.1	0.56
Stage 2 CKD	41.7	37.8	
Stage 3 CKD	7.8	5.4	
Stage 4 CKD	0.2	0.4	
Diuretic use (%)			
No diuretic use	70.2	67.2	0.3
Diuretic use	29.8	32.8	

[a]Significant P-value, $P < 0.05$. CKD: Chronic kidney disease; HCV: Hepatitis C virus; BMI: Body mass index.

those who did not in genotypes 2 (n = 48) and 3 (n = 40).

Figure 3 shows the rate of change in eGFR one-year after HCV treatment compared to one-year before treatment separated out by treatment type. In patients treated with dasabuvir, ombitasvir, paritaprevir, and ritonavir and ledipasvir/sofosbuvir, there was less of a decline in eGFR between one-year before HCV treatment compared to one-year after treatment in patients who achieved SVR12 compared to those who did not (P = 0.005). In patients treated with sofosbuvir, there was not statistically significant difference in the rate of change in eGFR between those achieved SVR12 compared to those who did not (P = 0.68) although the decline in eGFR was less in those who achieved SVR12.

DISCUSSION

In this single-center cohort of Veterans, we demonstrate that patients who achieved SVR12 with interferon-free DAAs had a reduced progression of renal disease that was statistically significant compared to patients who did not achieve SVR12. However, there were no significant differences in renal function decline between patients who were not treated with DAAs compared to

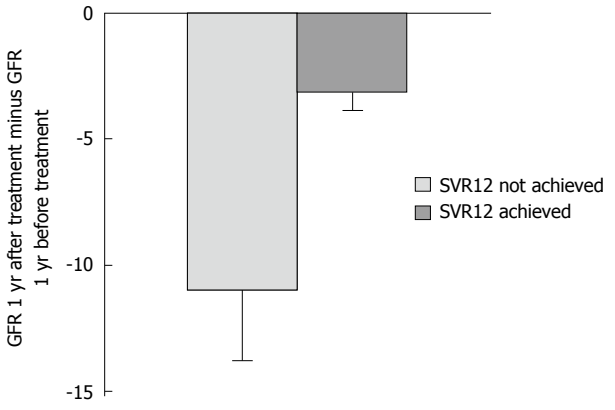

Figure 1 Rate of change in glomerular filtration rate one-year after hepatitis C virus treatment compared to one-year before treatment in relation to achievement of sustained virological response at 12 wk (*P* = 0.002). GFR: Glomerular filtration rate; SVR12: Sustained virological response at 12 wk following therapy.

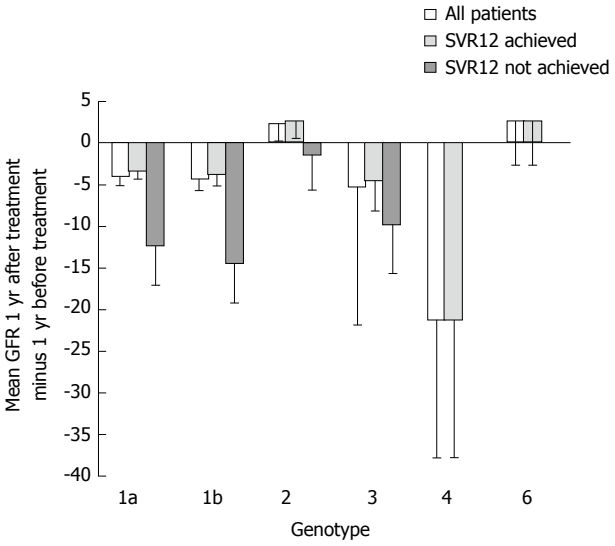

Figure 2 Rate of change in glomerular filtration rate one-year after hepatitis C virus treatment compared to one-year before treatment in relation to achievement of sustained virological response at 12 wk separated by genotype. GFR: Glomerular filtration rate; SVR12: Sustained virological response at 12 wk following therapy.

those who were treated and achieved SVR12.

While there appears to be an association between HCV infection and progression CKD, the mechanism of HCV-induced kidney injury continues to be debated. One hypothesis is that HCV triggers immune and inflammatory responses locally, within vascular tissues, or potentially systemically through inflammatory mediators, causing atherothrombosis and thus progression of CKD[11]. Immune complex deposition with HCV proteins and anti-HCV antibodies may provoke kidney injury[15]. HCV RNA and related proteins have been found in mesangial cells and the existence of these HCV-related proteins in the mesangium is associated higher proteinuria, which may suggest HCV infection causes direct mesangial injury[16]. Another thought is that HCV seropositive status induces accelerated

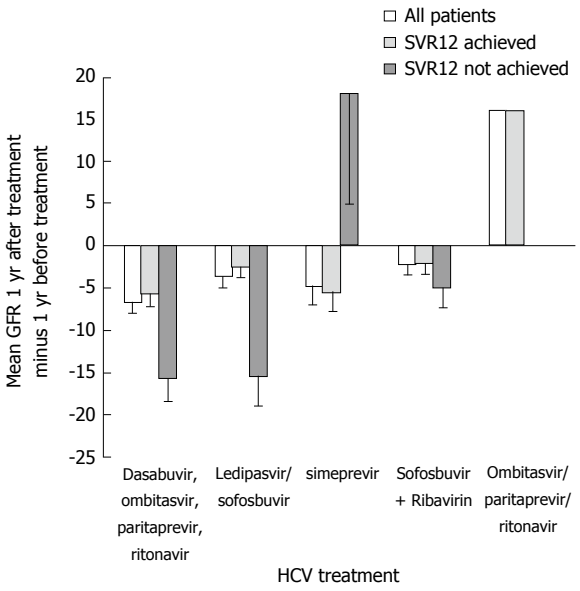

Figure 3 Rate of change in glomerular filtration rate one-year after hepatitis C virus treatment compared to one-year before treatment in relation to achievement of sustained virological response at 12 wk separated by hepatitis C virus treatment type. GFR: Glomerular filtration rate; SVR12: Sustained virological response at 12 wk following therapy; HCV: Hepatitis C virus.

atheromatous disease at the kidney level[11]. There is also clinical and laboratory evidence that suggests that HCV infection may be associated with insulin resistance and susceptibility to diabetes, which may lead to endothelial dysfunction and oxidative stress[11,17,18].

There was no significant difference in renal function decline between those who were treated for HCV and achieved SVR12 and those who were not treated for HCV. These results are similar to previous studies. A meta-analysis looking at the effect of antiviral therapy on HCV-associated CKD showed that HCV RNA clearance with interferon based therapy was not associated with a decrease in serum creatinine in the group that achieved SVR12 compared to the group that did not[19]. However, those who achieved SVR12 did have a decrease in protein excretion[19]. There was inadequate data on proteinuria, given the retrospective design and given proteinuria is infrequently ordered by physicians at our center, thus we were unable to determine the impact of SVR12 on proteinuria.

The fact that there were no significant differences in renal function decline between patients who were not treated with DAAs compared to those who were treated and achieved SVR12, suggests that viral eradication may not be associated improvement in the progression of renal disease. In patients with MPGN and type Ⅱ cryoglobulinemia, there may be virological clearance with DAA therapy, but there may be persistence of cryoglobulinemia, which may lead to persistent renal decline. Circulating cryoglobulins are detected in a large number of patients with HCV, however, only a minority of patients will experience clinical manifestations, thus some cases of cryoglobulinemia may remain undetected[20]. A recent study by Emery *et al*[21], showed that despite

high SVR rates after DAA treatment in patients with HCV associated mixed cryoglobulinemia only 29.4% of symptomatic patients had complete cryoprecipitate clearance despite achievement of SVR12. Work by Gragnani *et al*[22] showed a 100% SVR12 rate, however reported that only 34% of patients had full complete response, defined as disappearance of all the baseline symptoms, with follow-up to 24 wk. However, a recent case series suggests that in patients with HCV and mixed cryoglobulinemia syndrome treated with DAAs that there is an improvement in renal function, even in patients not concomitantly treated with immunosuppression[23].

Another explanation as to why achievement of SVR12 may not improve renal disease progression is that patients may have intrinsic renal disease prior to treatment, such as MPGN, and these patients will have CKD progression despite achieving SVR12; this has been previously described in the literature in case reports[24]. However, other reports have suggested that DAA therapy can result in successful treatment of HCV-associated MPGN with improvement in creatinine and proteinuria[25]. Furthermore, the patient population studied was unique - it is comprised of Veterans who are predominantly male, older in age, have a higher prevalence of CKD compared to the general population, and often have significant co-morbidities associated with CKD, such as diabetes mellitus, hypertension, vascular disease, and cancer[26]. Given the high prevalence of CKD and associated co-morbidities in this veteran population, CKD progression may have occurred despite SVR12 given the other presence of co-morbidities that drive CKD progression.

An alternative explanation could also be that although HCV clearance may have renal sparing effects, there many be a component of direct nephrotoxicity due to DAA therapy. In patients treated with Viekira or ledipasvir and sofosbuvir, there was a greater decline in eGFR in those who did not achieve SVR12 compared to those who achieved SVR12. However, the sample sizes for each treatment group are too small to make any definitive conclusions. Previous treatment with interferon-based therapy was associated with acute kidney injury, however kidney injury has not been attributed to any DAA therapy[27]. Sofosbuvir's circulating metabolite GS-331007 is renally cleared, thus there is a concern of Sofosbuvir use in patients with eGFR < 30 mL/min, but further work is needed to investigate the cases of kidney injury in patients following Sofosbuvir treatment[28].

There is a greater decline in renal function in those who were treated with DAAs and did not achieve SVR12 compared to those who were never treated. However, the group that did not achieve SVR12 following treatment had a greater proportion of cirrhotic patients when compared to the control group who did not undergo treatment. Given that the group who did not achieve SVR12 had a greater proportion of patients with cirrhosis, this group may have been more ill and thus had a higher propensity to undergo complications, such as hepatorenal syndrome, which may contribute to worsening renal function.

Our study has a number of limitations. First, this is a single center study restricted to Veteran health care users; therefore, the results may not be generalizable to non-Veteran populations, given the higher prevalence of baseline CKD and only a few women. Its retrospective nature may result in bias due to confounding variables, including unmeasured patient characteristics. The Modification of Diet in Renal Disease (MDRD) equation used to estimate GFR might be less accurate among patients in hepatitis C and cirrhosis because of abnormalities in protein metabolism as well as muscle wasting. In patients with cirrhosis, serum creatinine is a poor measure of GFR, however it is often used as a surrogate marker[29,30]. Finally, our follow-up time was short due to the recent introduction of DAAs. For our treatment cohort, there was not enough eGFR data two years following treatment, thus we were only able to evaluate eGFR changes one year following treatment. It is possible that the strength and degree of the associations described in the study might differ if the follow up period was extended.

Our study may have implications for clinical practice. Clinicians may be prompted to discuss the need for ESRD surveillance in their patients with HCV prior to treatment with DAAs. The current KDIGO guidelines suggest the patients with HCV be tested annually for proteinuria and eGFR, however the guideline is rated weak given it is based on expert judgment[31]. Given the lack of strong guidelines, it is likely that patients with HCV are not being screened for ESRD.

In summary, we found that there was a lesser decline in renal function in patients who achieved SVR12 compared to those who did not, however there were no significant differences in renal function decline between patients who were not treated compared to those who were treated and achieved SVR12. Additional research is needed to confirm these results in multi-institutional studies with longer duration of follow-up. Further work is required to develop screening guidelines for kidney disease in patients with HCV.

ARTICLE HIGHLIGHTS

Research background

Hepatitis C virus (HCV) is a significant public health issue in the United States and worldwide. The consequences of HCV infection extend beyond the liver, including renal complications. Patients with HCV are at risk for renal function decline and developing end-stage renal disease (ESRD). Chronic kidney disease (CKD) is an important public health problem as it increases the likelihood of adverse outcomes and is associated with high healthcare costs.

Research motivation

Given HCV infection places patients at risk for renal function decline and developing ESRD, it is valuable to understand how the clearance of HCV infection with interferon free, direct acting antiviral (DAA) therapy affects chronic kidney progression. Given the recent introduction of DAA therapy, the impact of HCV clearance on kidney disease has not been fully established.

Research objectives

The authors' principal aim was to determine if the achievement of sustained virological response at 12 wk (SVR12) with interferon-free, DAAs impacts the progression of CKD.

Research methods

The authors retrospectively analyzed medical records of adult patients who initiated hepatitis C treatment with interferon-free DAAs from 2014 to 2016 at the VA Greater Los Angeles Healthcare System. The control group consisted of adult patients who did not undergo hepatitis C treatment, prior to the introduction of DAAs, from 2011 to 2013. Baseline demographic and clinical data were collected. The rate of change in estimated glomerular filtration rate (eGFR) one-year after HCV treatment compared to one-year before treatment was compared between patients who achieved SVR12 to those who did not. The change in eGFR was recorded over two years in patients who did not undergo treatment and compared to those who underwent DAA treatment.

Research results

The findings of the analysis suggest that patients who achieved SVR12 with interferon-free DAAs had a reduced progression of renal disease that was statistically significant compared to patients who did not achieve SVR12. However, there were no significant differences in renal function decline between patients who were not treated with DAAs compared to those who were treated and achieved SVR12. The control group was not statistically different from the cohort of HCV treated patients, except that the there were significantly more patients with cirrhosis and obesity in the cohort who underwent HCV treatment compared to the control group. The control group, however, had significantly more patients with hypertension and congestive heart failure compared to the cohort who underwent HCV treatment.

Research conclusions

There is a lesser decline in renal function in patients who achieved SVR12 compared to those who did not, however there were no significant differences in renal function decline between patients who were not treated compared to those who achieved SVR12. There are several possible explanations for the lack of improvement of CKD progression with viral eradication, such as immune factors related to cyroglobulins, intrinsic renal disease prior to therapy, and that the control group had significantly more patients with cirrhosis compared to the treatment group.

Research perspectives

Additional research is needed to confirm these results in multi-institutional studies with longer duration of follow-up.

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CASE REPORT

De-novo hepatocellular carcinoma after pediatric living donor liver transplantation

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Abstract

De-novo malignancies carry an incidence ranging between 3%-26% after transplant and account for the second highest cause of post-transplant mortality behind cardiovascular disease. While the majority of *de-novo* malignancies after transplant usually consist

of skin cancers, there has been an increasing rate of solid tumor cancers over the last 15 years. Although, recurrence of hepatocellular carcinoma (HCC) is well understood among patients transplanted for HCC, there are increasing reports of *de-novo* HCC in those transplanted for a non-HCC indication. The proposed pathophysiology for these cases has been mainly connected to the presence of advanced graft fibrosis or cirrhosis and always associated with the presence of hepatitis B or C virus. We report the first known case of *de-novo* HCC in a recipient, 14 years after a pediatric living related donor liver transplantation for end-stage liver disease due to biliary atresia without the presence of hepatitis B or C virus before and after transplant. We present this case report to increase the awareness of this phenomenon and address on the utility for screening and surveillance of hepatocellular carcinoma among these individuals. One recommendation is to use similar guidelines for screening, diagnosis, and treatment for HCC as those used for primary HCC in the pre-transplant patient, focusing on those recipients who have advanced fibrosis in the allograft, regardless of etiology.

Key words: Liver transplantation; *De-novo* hepatocellular carcinoma; Living donor liver transplantation; Biliary atresia

Core tip: *De-novo* hepatocellular carcinoma (HCC) is a rare event compared to other *de-novo* malignancies, although the number of reported cases are increasing. The pathophysiology has been related with advanced graft fibrosis, cirrhosis and hepatitis viral serology. We report the first case of *De-novo* HCC 14 years after living related donor liver transplantation for end-stage liver disease due to biliary atresia without positive hepatitis B or C viral serology. Current screening and treatment guidelines have not been well established. This increasing phenomenon challenges us to define the utility of screening and surveillance for hepatocellular carcinoma in these individuals.

Torres-Landa S, Munoz-Abraham AS, Fortune BE, Gurung A, Pollak J, Emre SH, Rodriguez-Davalos MI, Schilsky ML. *De-novo* hepatocellular carcinoma after pediatric living donor liver transplantation. *World J Hepatol* 2017; 9(36): 1361-1366 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i36/1361.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i36.1361

INTRODUCTION

Hepatocellular carcinoma (HCC), the most common primary malignancy of the liver, is one of the most lethal and prevalent cancers worldwide. However, the use of liver transplantation (LT) is a well proven treatment approach for patients with low stage tumor. The pathogenesis of HCC typically involves chronic liver injury with regeneration, fibrosis and cirrhosis leading to dysplasia within regenerating nodules with an end result of malignancy[1]. HCC development in a liver allograft occurs most often in the setting of prior HCC where it is defined as recurrence[2]. *De-novo* tumor formation that arises in the transplanted graft without evidence of tumor in the previously explanted liver is uncommon and is mainly seen in patients with advanced graft fibrosis or cirrhosis and associated with the presence of hepatitis B or C viral infection[3]. The literature reveals only 15 documented cases of *de-novo* HCC after LT[4-15]. We report the first case of *de-novo* HCC occurring 14 years after a pediatric patient received a living related donor LT for end stage liver disease secondary to biliary atresia.

CASE REPORT

A 29-year-old male with a history of biliary atresia with failed Kasai procedure complicated with progressive cirrhosis and portal hypertension that received a left lateral segment living donor liver transplant (LDLT) from his biological father at 15 years of age. His immunosuppressive regimen included tacrolimus, and sirolimus. Eleven years after his LDLT, he developed advanced liver fibrosis and portal hypertension that manifested as refractory ascites. He received a splenectomy and a central spleno-renal shunt that eventually failed. He then underwent a side-to-side porto-caval shunt (PCS) at age 27 years. After 2 years with controlled disease, he presented with recurrent ascites and overt hepatic encephalopathy (HE) related to his progressive graft failure. His clinical course was also complicated by severe protein losing enteropathy due to his worsening portal hypertension (sprue was excluded by small bowel biopsy). Other causes of hypoalbuminemia were ruled out (*e.g.,* kidney injury secondary sirolimus, as evidenced by 24-h urine collection with minimal protein and normal creatinine). Liver biopsy at this time showed stage 3-4 fibrosis. In addition, there was a paucity of interlobular bile ducts with degenerative changes in the remaining ducts, features compatible with chronic allograft rejection. A few months after, an abdominal ultrasound of the graft revealed a hepatic mass measuring 2.9 cm × 2.2 cm located in segment 2/3 and no evidence of intrahepatic duct dilation. Dynamic CT imaging showed a 3 cm lesion in the left lateral segment that was slightly hypodense and indeterminate in nature (Figure 1). A dynamic magnetic resonance imaging (MRI) using liver mass protocol was performed due to the indeterminate nature of the lesion on CT and demonstrated increased vascularity of the lesion, raising suspicion for HCC. An ultrasound-guided percutaneous biopsy of the mass revealed a well-differentiated HCC (Figure 2). Chest CT scan and bone scan demonstrated no evidence of extra hepatic disease. Alpha-fetoprotein (AFP) level was slightly elevated at 17 ng/mL (normal < 6 ng/mL).

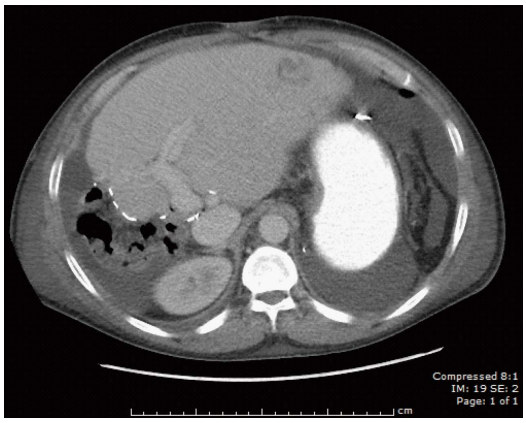

Figure 1 Dynamic computerized tomography scan imaging showing indeterminate 3 cm lesion in the left lateral segment.

Anti-HBcAb (anti-hepatitis B core total antibodies) at this time and a year before showed negative results. The lesion was subsequently treated by percutaneous microwave ablation (PMWA).

Follow up MRI was performed 1.5 mo after the ablation and showed no residual tumor (Figure 3). The patient was subsequently listed for repeat liver transplantation. However, while on the wait-list he developed a second post-transplant malignancy, an EBV negative Burkitt's type lymphoma. He received chemotherapy for the lymphoma but succumbed to complications due to the treatment that was in part limited by his advanced liver disease.

DISCUSSION

Liver transplantation provides the highest survival rates among patients with decompensated cirrhosis and complications of portal hypertension but recipients have a 2-4 fold increased risk of developing *de-novo* malignancies when compared to matched healthy controls[16]. *De-novo* malignancies represent 30% of post-transplant deaths and one of the most common causes of death in patients that survive beyond a year after transplantation[3,17]. Although there is an increased risk of developing malignancies, *De-novo* HCC is uncommon[3,17].

When HCC after transplantation is identified, it is crucial to know if it is a recurrent malignancy as this carries a poor prognosis. Travesani *et al*[17] have proposed an algorithm where they suggest suspicion primary features of a recurrent case including lymph node invasion, macro and microvascular invasion, tumor size > 5 cm, high grade tumor, bi-lobar involvement and high alpha fetoprotein levels. Secondary features include early occurrence, < 2 years, and extra hepatic localization. Without the presence of these characteristics, the suspicion turns towards a *de-novo* HCC. Other common clinical factors that suggest a *de-novo* case, even in patients transplanted for or with a previous HCC, are older donor age, alcoholic liver disease, viral hepatitis,

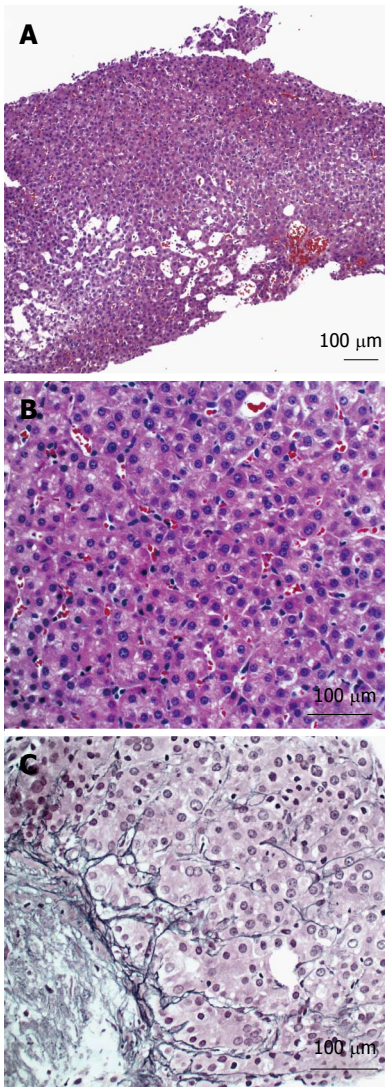

Figure 2 Ultrasound-guided liver biopsy. A: Biopsy of the mass shows a solid growth pattern of hepatocytes (H+E, 100 ×); B: Neoplastic hepatocytes contain hyperchromatic, pleomorphic and enlarged nuclei (H+E, 200 ×); C: Reticulin stain demonstrates thickened trabeculae and decreased staining in the lesion (200 ×).

recurrent liver disease and exposure to environmental carcinogens. Although the clinical features cannot guarantee the distinction with certainty, molecular techniques may permit differentiation of donor from recipient origin[17]. In addition, allografts have a certain degree of hepatocyte chimerism (graft and recipient cells) that also correlates with the degree of hepatic injury and is strongly associated with hepatitis[18].

The pathogenesis of HCC appears to be related to chronic hepatic inflammation that eventually leads to fibrosis and cirrhosis. The inflammatory microenvironment in the liver leads to a proliferative state that can promote dysplasia and eventually malignancy regardless of the underlying liver disease[1]. Graft rejection, which is an immunological surge against detected antigens found within the graft, can generate a chronic inflammatory state[19] and create an environment that promotes oncogenesis and dysplasia. Other well-established risk

Table 1 Modified from Saab *et al*[14]

Patient	Ref.	OLT indication	Age	Gender	Immunosuppression	Interval (yr)	Type of donor	PVS	Approach after *de-novo* HCC
1	Saxena *et al*[4]	HCV and ALD	63	M	CYA, AZA and Pred	7	DD	Yes	Retransplant
2	Levitsky *et al*[5]	HCV and ALD	48	M	CYA, AZA and Pred	5	N/A	Yes	NR
3	Croitoru *et al*[6]	HCV and NAFLD	61	M	CYA and Pred	6	DD	Yes	Retransplant
4	Flemming *et al*[7]	HBV	NR	M	NR	9	DD	Yes	Hepatic Resection
5	Flemming *et al*[7]	HBV	NR	M	NR	8	DD	Yes	Retransplant and Hepatic Resection
6	Torbenson *et al*[8]	HBV	51	M	NR	8.5	DD	Yes	Retransplant
7	Kita *et al*[9]	HBV	43	M	NR	14	NA	Yes	Retransplant
8	Yu *et al*[10]	HBV	36	M	TAC, MMF andPred	2	LD	Yes	RFA
9	Sotiropoulos *et al*[11]	Budd-Chiari Syndrome	61	F	NR	22	NA	Yes	TACE
10	Sotiropoulos *et al*[11]	ALD	65	M	NR	5	NA	NR	RFA
11	Vernadakis *et al*[12]	ALD	59	M	CYA, MMF and Pred	3	DD	No	Hepatic Resection
12	Tamè *et al*[13]	HCV	54	M	TAC and Pred	6	DD	Yes	TACE
13	Saab *et al*[14]	HCV	47	F	TAC and MMF	19	-	Yes	TACE, RFA, Sorafenib, Retransplant
14	Tamè *et al*[13]	SSC	44	M	TAC and Pred	6	DD	Yes	Sorafenib
15	Navarro Burgos *et al*[15]	HCV and HBV	45	M	NR	0.75	DD	Yes	TACE
16	The present case	Biliary atresia	29	M	TAC and Sirolimus	14	LD	No	PMWA

OLT: Orthotropic liver transplantation; DD: Deceased donor; LD: Living donor; PVS: Positive viral serology; HCV: Hepatitis C virus; SSC: Secondary sclerosing cholangitis; ALD: Alcoholic liver disease; NAFLD: Non-alcoholic fatty liver disease; HBV: Hepatitis B virus; NR: Not reported; CYA: Cyclophosphamide; AZA: Azathioprine; Pred: Prednisone; TAC: Tacrolimus; MMF: Mycophenolate mofetil; RFA: Radiofrequency ablation; TACE: Transarterial chemoembolization; PMWA: Percutaneous microwave ablation; M: Male; F: Female; NA: Not available.

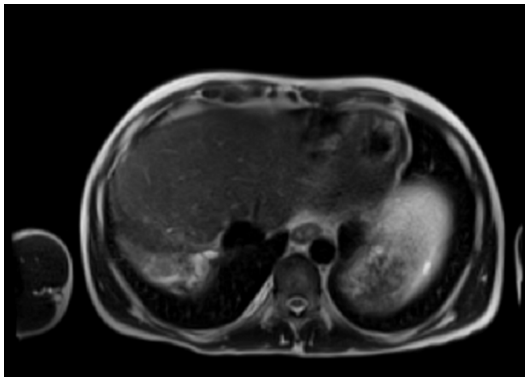

Figure 3 Follow-up magnetic resonance imaging showing the ablation cavity in segment III measuring 2.8 cm × 2.5 cm without evidence of residual tumor.

factors for promoting carcinogenesis include the use of immunosuppressive therapy as it reduces immune surveillance, increased age and gender specific cancer risks, development of insulin resistance and exposure to viral infections (HBV and HCV)[3,16,17].

From the 16 cases of *de-novo* HCC occurrence reported so far in the literature, 14 had positive viral serology (HVB or HCV) (Table 1). In these cases the viral infection likely drove tumorogenesis. However, this is a novel case describing a *de-novo* HCC after a LDLT in a pediatric patient. Our case represents the development of a hepatic tumor in the setting of advanced hepatic fibrosis, likely from chronic allograft rejection, without any underlying viral disease or other chronic infection. Interestingly both biliary atresia itself and Kasai procedure have been associated with the development of HCC[20-22]. However, given the 14 year gap from transplant to development of HCC, this probably did not contribute to the development of HCC in this particular patient.

Although current treatment guidelines for *De-novo* HCC after LT have not been well established, it was suggested that these cases be approached according to the current guidelines for primary and recurrent HCC[17]. The strategies that have been used in the reported cases to date are: re-transplantation (n = 6)[4,6-9,14], trans-arterial chemoembolization (TACE) (n = 4)[11,13-15], hepatic resection (n = 3)[7,12], radiofrequecy ablation (RFA) (n = 3)[10,11,14], medical therapy with Sorafenib (n = 2)[13,14] and PMWA in our case. Two of the reported cases used more than one procedure[7,14].

Proper age and gender appropriate cancer screening and surveillance is universally practiced among transplant recipients to diagnosis early stage malignancy. Since approximately one-fifth of all post-transplant deaths are related to *de-novo* neoplasms (including *de-novo* HCC)[3] and the incidence of HCC recurrence can be as high as 18.3% after transplant[2], many transplant programs have in place post-LT screening and surveillance for HCC in patients transplanted for HCC along with other

appropriate cancer screening and surveillance[3]. However, these protocols for post-LT screening and surveillance are not uniform amongst centers as there is a general lack of evidence base for deciding on a specific protocol. This remains to be established.

In summary, we describe the first case of *de-novo* HCC after living donor liver transplantation in a patient with a prior history of biliary atresia who developed graft dysfunction and complications of portal hypertension. This case and the increase in reports of *de-novo* development of HCC in liver grafts of patients without HCC prior to LT challenges us to define the incidence of development of HCC in post-LT patients with chronic injury and graft fibrosis to determine when there is utility in recommending screening and surveillance of these individuals for HCC, and design appropriate protocols to carry this out.

ARTICLE HIGHLIGHTS

Case characteristics

A 29-year-old male with a history of biliary atresia with failed Kasai procedure complicated with progressive cirrhosis and portal hypertension that received a left lateral segment living donor liver transplant (LDLT) from his biological father at 15 years of age.

Clinical diagnosis

Biliary atresia, complicated with progressive cirrhosis and portal hypertension that received a left lateral segment living donor liver transplant LDLT.

Differential diagnosis

A case of *de-novo* hepatocellular carcinoma (HCC) (confirmed by ultrasound-guided percutaneous biopsy of the mass) 14 years after a pediatric living related donor liver transplantation for end-stage liver disease without positive hepatitis B or C viral serology.

Imaging diagnosis

Follow up magnetic resonance imaging was performed 1.5 mo after the ablation and showed no residual tumor.

Treatment

The lesion was subsequently treated by percutaneous microwave ablation. The patient was subsequently listed for repeat liver transplantation. Current screening and treatment guidelines have not been well established.

Experiences and lessons

This increasing phenomenon challenges us to define the utility of screening and surveillance for HCC in these individuals.

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CASE REPORT

Autoimmune hepatitis in the setting of human immunodeficiency virus infection: A case series

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Abstract

Liver injury in the setting of human immunodeficiency virus (HIV) infection is more commonly attributed to viral hepatitis or highly active antiretroviral treatment (HAART) toxicity. The severity of liver injury is an important cause of morbidity and mortality. The emergence of autoimmune diseases, particularly autoimmune hepatitis (AIH) in the setting of HIV infection, is rare. Previous reports indicate that elevated liver enzymes are a common denominator amongst these patients. We present two patients with HIV infection, on HAART, with virological suppression. Both patients presented with elevated liver enzymes, and following liver biopsies, were diagnosed with AIH. The clinical course of these patients underscore the therapeutic value of corticosteroids, and in some cases, addition of immunosuppression for AIH treatment.

Key words: Liver biopsy; Human immunodeficiency virus; Immunosuppression; Autoimmunity; Autoimmune hepatitis

Core tip: Liver damage is rarely caused by autoimmune disease in the setting of human immunodeficiency virus (HIV) infection. We describe a case series of two patients with a history of HIV, who presented with characteristic elevation in liver enzymes. Both

patients were hepatitis C negative. Liver biopsies followed by histopathology confirmed the diagnosis of autoimmune hepatitis. Case 1 was treated by corticosteroids and azathioprine, while case 2 was treated by corticosteroids only. Both patients reported significant clinical improvement. These cases suggest that liver biopsy should be performed in HIV patients with unknown liver disease. Additionally, they underscore the need for further clinical studies to explore the role of corticosteroids and immunosuppression in the management of autoimmune hepatitis in HIV patients.

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INTRODUCTION

Autoimmune hepatitis (AIH) is a rare chronic liver disease which was first reported in the 1950s by the Swedish physician Jan Waldstrom[1]. Patients infected with human immunodeficiency virus (HIV) tend to have impaired immune systems, weakening host defenses against opportunistic pathogens, and autoimmunity[2]. Given that complications of liver disease in the setting of HIV are more likely due to coinfections with hepatitis B (HBV) or hepatitis C (HCV) viruses, antiretroviral drug toxicity, opportunistic infections, or neoplastic disorders, it is very rare to encounter cases of AIH. While the global occurrence of AIH is largely unknown, in Europe and North America it has been estimated at 1.9/100000 incidence and 16.9/100000 prevalence[3]. A review of the literature shows that only 18 cases (excluding our two patients) have been reported[4-11]. Herein, we present two cases of AIH in the setting of HIV infection.

CASE REPORT

Case 1

A 40-year-old male who emigrated from Guyana, diagnosed with HIV since 2009 and started on efavirenz, emtricitabine, and tenofovir disoproxil fumarate (Atripla), with viral suppression and immunological recovery (CD4 cell count 832/mm^3), presented for a follow-up. He was a non-smoker with prior history of alcohol consumption and liver cirrhosis. Laboratory workup showed elevated liver enzymes of alanine aminotransferase (ALT) 302 U/L, and aspartate aminotransferase (AST) 149 U/L. These values decreased over the next 3 mo and increased again, reaching their highest at 14 mo: ALT 465 U/L, and AST 302 U/L. Alkaline phosphatase (ALP) was elevated at 233 U/L, total bilirubin 1.3 mg/dL, direct bilirubin 0.6 mg/dL, and alpha-fetoprotein (AFP) 14 ng/mL.

To elucidate the etiology of elevated transaminases, further laboratory tests were performed. He was immune to HBV virus, nonreactive for HCV antibody and undetected by quantitative PCR assay. White cell count, hemoglobin, hematocrit, platelets, prothrombin time, INR, and albumin were all within normal limits. Iron and copper metabolism in addition to ceruloplasmin and alpha-1-antitrypsin levels were also normal. Autoimmune assay for antinuclear antibodies (ANA) was negative, and smooth muscle antibody (ASMA) immunoglobulin G (IgG) was positive at 60 Units (normal 0-19 Units), suggestive of autoimmune hepatitis. Hemochromatosis gene mutations (H63D and C282Y) screening were negative. IgG level was 2740 mg/dL.

Abdominal ultrasound showed a normal sized liver with slight heterogeneity, suggestive of diffuse liver disease. Abdominal magnetic resonance imaging (MRI) showed obstruction of the right hepatic tip by a blooming artifact of uncertain etiology. A transthoracic percussion guided liver biopsy was performed without complications. Histopathology showed fibrous portal expansion and bridging fibrosis. Portal and periportal inflammatory activity along with piecemeal necrosis was identified (Figure 1). Taken in clinical context, the diagnosis of AIH was confirmed. The patient was started on corticosteroids, and was later prescribed Azathioprine.

The patient was lost to follow-up, but presented 18 mo later and showed a notable improvement in liver enzymes: ALT 112 U/L, and AST 81 U/L. He reported no new symptoms related to liver disease. However, the patient was non-compliant with his medications and repeated laboratory results showed rising liver transaminases again (Figure 2A). The patient was advised to restart his medications.

Case 2

A 44-year-old Hispanic female diagnosed with HIV since 1997 and started on Atripla since 2010 with viral suppression and immunological recovery (CD4 count 823, and viral load undetectable), was admitted for epigastric pain and vomiting. A non-smoker, laboratory workup showed elevated liver chemistries: ALT 155 U/L, AST 136 U/L, ALP 100 U/L, total bilirubin 1.9 mg/dL, AFP 16 ng/mL. She was immune to Hepatitis A (HAV) and HBV, and non-reactive for HCV. ANA (1:640), and ASMA (1:180), were positive suggestive of AIH. Abdominal MRI showed perihepatic fluid and cirrhosis of the liver. Esophagastroduodenoscopy (EGD) revealed a gastric ulcer, which was positive for *Helicobacter pylori* (*H. pylori*) gastritis. Colonoscopy revealed a tubular adenoma. The patient was stabilized and discharged after 6 d.

A liver biopsy was performed without complications. Histopathology showed confluent necrosis infiltrated by dense lympho plasmacytic infiltrates partially replaced by fibrous tissue, as well as bridging fibrous septa that enclosed regenerative nodules, consistent with AIH. The patient was started on prednisone. At the 6th week of steroid therapy, the patient reported notable

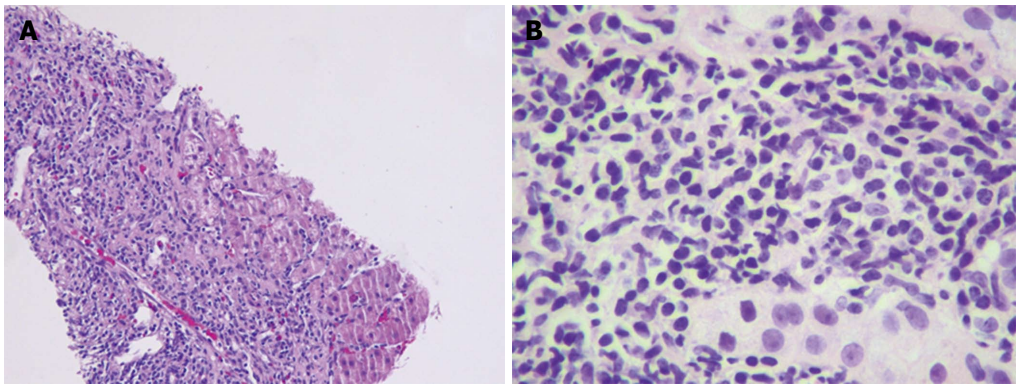

Figure 1 Microscopic examination. A: Microscopic examination reveals mild portal/periportal chronic inflammation; B: Microscopic examination reveals moderate chronic inflammation in a background of cirrhosis. Original magnification, × 20 (A), and × 40 (B).

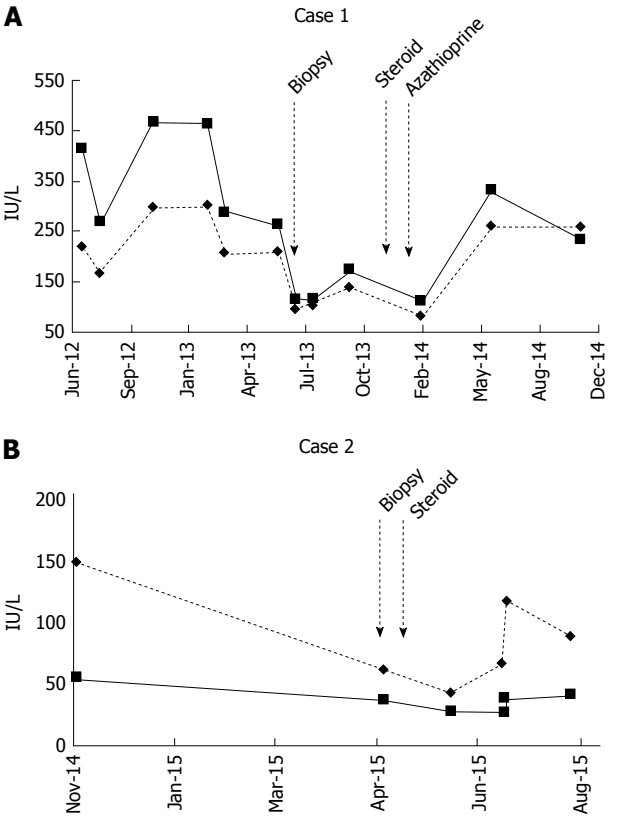

Figure 2 Graphical representation of alanine transferase (straight line) and aspartate transaminase (dashed line) over time (A and B). Time of biopsy and treatment also denoted.

improvement in symptoms, and resolving liver enzyme levels (Figure 2B).

DISCUSSION

HIV is associated with the development of autoimmune disorders such as immune thrombocytopenic purpura, inflammatory myositis, sarcoidosis, Guillain Barre Syndrome, myasthenia gravis, Graves' disease, systemic lupus erythematosus, rheumatoid arthritis, Hashimoto thyroiditis, autoimmune hemolytic anemia, and very rarely, autoimmune hepatitis[12]. Due to its rarity, AIH in the setting of HIV is not often suspected by clinicians, but should be considered when all other etiologies are ruled out.

There are two clinically relevant types of AIH; namely, type 1 and type 2. Type 1 AIH is referred to as the classic type, typically diagnosed in adulthood, whereas type 2 is diagnosed during childhood[13,14]. Though both types are similar, type 2 AIH can be more severe and difficult to manage. Symptoms associated with AIH include fatigue, pruritus, jaundice, nausea, vomiting, abdominal pain, weight loss, light colored stools, dark colored urine, joint pain, rashes, and loss of menstruation in women[4-11,15,16]. Without adequate therapy, the disease can progress in the form of liver fibrosis. As a result, patients can develop cirrhosis, liver failure, ascites, gastrointestinal bleeding, hepatic encephalopathy, and even hepatocellular carcinoma.

The diagnosis of AIH is established based on the following criteria by the American and European practice guidelines: Hyper-gammaglobulinemia, positive serologic tests including antinuclear and anti-smooth muscle antibodies, and a characteristic hepatic histological appearance, namely interface hepatitis, plasmacytic infiltrate, and regenerative liver-cell rosettes[17]. Other liver diseases such as alpha-1-antitrypsin deficiency, Wilson disease, hemochromatosis, viral hepatitis, drug-induced liver injury, and alcoholic/nonalcoholic liver disease should be ruled out.

The diagnosis of AIH in HIV infected patients pose a diagnostic conundrum because HIV infection is usually considered as being protective against autoimmunity. However, several mechanisms have been proposed by which HIV may subvert and influence host immune regulation. Firstly, it is thought that viral infection triggers a pro-inflammatory milieu, which overrides host regulatory networks. This may lead to the generation of self-perpetuating autoimmune reactions[18]. Genetic susceptibility has also been proposed as an alternative mechanism. AIH is a polygenetic disorder with strong evidence of inheritability. During the maturation of T-cells, the thymus deletes T-cells that react too strongly to self-antigens[19]. Thymic mutations can indeed affect this process and lead to AIH. Furthermore, despite thymic selection, individuals who express HLA haplotypes DR3,

DR4, and hepatocyte enzyme CYP2D6, are more likely to develop AIH[20-23].

Another suggested mechanism is the role of immune reconstitution inflammatory syndrome (IRIS), also known as immune restoration disease. While the pathogenesis of IRIS is speculative, it is thought to occur in patients with significant increase in CD4 cells after initiation of anti-retroviral (ARV) therapy, specifically those who concurrently had low CD4 cells prior to treatment[24,25]. It has been noted that the increase in CD4 count may not be responsible for the inflammatory response, but instead may be due to preexisting perturbations in T-regulatory cells (Tregs), and proinflammatory and regulatory responses such as cytokine imbalances that may significantly contribute to the onset of the syndrome after the initiation of ARV therapy[26].

As far as we know, there are no guidelines for the treatment of AIH in HIV patients. A review of published cases showed that corticosteroids and immunosuppression were reasonably used by other clinicians[4-11]. Case 1 involved the use of corticosteroids and azathioprine, while case 2 used corticosteroids only. While both cases showed resolution of symptoms, it also suggested that additional immunological suppression with azathioprine may not be required for treating AIH.

In conclusion, AIH is a rare and chronic liver disease which seldom presents in HIV-infected patients. A characteristic elevation in liver enzymes is commonly reported in these cases. However, they are often attributed to HAART or other possible liver diseases, particularly viral hepatitis. For this reason, liver biopsies should be performed in HIV patients with an unknown liver disease etiology. Furthermore, patients with AIH in the setting of HIV infection should be treated with corticosteroids. Further research is needed to study the efficacy of corticosteroids with or without the use of immunosuppression.

ARTICLE HIGHLIGHTS

Case characteristics

Case 1: A 40-year-old male diagnosed with human immunodeficiency virus (HIV) since 2009 and started on Atripla, with viral suppression and immunological recovery, presented for a follow-up. Case 2: A 44-year-old Hispanic female diagnosed with HIV since 1997 and started on Atripla since 2010, with viral suppression and immunological recovery, was admitted for epigastric pain and vomiting.

Clinical diagnosis

Case 1: Abdominal ultrasound showed a normal sized liver with slight heterogeneity, suggestive of diffuse liver disease. Case 2: An abdominal magnetic resonance (MRI) imaging was suggestive of cirrhosis of the liver.

Differential diagnosis

Liver cirrhosis, hepatitis, hepatocellular carcinoma.

Laboratory diagnosis

Case 1: Laboratory workup showed elevated liver chemistries: Alanine aminotransferase (ALT) 302 U/L, and aspartate aminotransferase (AST) 149 U/L, alkaline phosphatase 233 U/L, total bilirubin 1.3 mg/dL, direct bilirubin 0.6 mg/dL, and alpha-fetoprotein 14 ng/mL. Case 2: Laboratory workup showed elevated liver chemistries: ALT 155 U/L, AST 136 U/L, alkaline phosphatase 100 U/L, total bilirubin 1.9 mg/dL, and alpha-fetoprotein 16 ng/mL.

Imaging diagnosis

Abdominal MRI imaging was suggestive of liver cirrhosis of uncertain etiology.

Pathological diagnosis

Case 1: A transthoracic percussion guided liver biopsy showed fibrous portal expansion, bridging fibrosis, and portal and periportal inflammatory activity with piecemeal necrosis, consistent with autoimmune hepatitis (AIH). Case 2: Liver biopsy showed confluent necrosis infiltrated by dense lymphoplasmacytic infiltrates partially replaced by fibrous tissue, as well as bridging fibrous septa that enclosed regenerative nodules, consistent with AIH.

Treatment

Case 1 was treated with corticosteroids and azathioprine, while case 2 was treated with corticosteroids only.

Related reports

Review of the literature shows that only 18 cases (excluding our two patients) have been reported.

Term explanation

The occurrence of autoimmune hepatitis in the setting of HIV-infected patients is an extremely rare clinical entity. The global prevalence of AIH is largely unknown. Currently, there are no standardized treatment for AIH.

Experiences and lessons

This report suggest that liver biopsies should be performed in HIV patients with an unknown liver disease etiology. HIV patients diagnosed with AIH should be treated with corticosteroids. Further research is needed to study the clinical efficacy of corticosteroids with or without the use of immunosuppression.

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CASE REPORT

Sequential tumor-directed and lobar radioembolization before major hepatectomy for hepatocellular carcinoma

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Author contributions: Degrez T, Bouazza F, Delatte P, Gomez Galdon M, Hendlisz A and Flamen P performed research; Vouche M and Donckier V performed research and wrote the paper.

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Abstract

Preoperative radioembolization may improve the resectability of liver tumor by inducing tumor shrinkage, atrophy of the embolized liver and compensatory hypertrophy of non-embolized liver. We describe the case of a cirrhotic Child-Pugh A patient with a segment Ⅳ hepatocellular carcinoma requiring a left hepatectomy. Preoperative angiography demonstrated 2 separated left hepatic arteries, for segment Ⅳ and segments Ⅱ-Ⅲ. This anatomic variant allowed sequential radioembolizations, delivering high-dose ^{90}Yttrium (160 Gy) to the tumor, followed 28 d later by lower dose (120 Gy) to segments Ⅱ-Ⅲ. After 3 mo, significant tumor

response and atrophy of the future resected liver were obtained, allowing uneventful left hepatectomy. This case illustrates that, when anatomic disposition permits it, sequential radioembolizations, delivering different ^{90}Yttrium doses to the tumor and the future resected liver, could represent a new strategy to prepare major hepatectomy in cirrhotic patients, allowing optimal tumoricidal effect while reducing the toxicity of the global procedure.

Key words: Hepatocellular carcinoma; Cirrhosis; Resectability; Radioembolization; Sequential; Efficacy; Safety

Core tip: Preoperative radioembolization may improve resectability of hepatocellular carcinoma in cirrhotic patient, inducing tumor downsizing, atrophy of radio-embolized sector and regeneration of non-embolized liver. We describe a patient with a segment Ⅳ hepatocellular carcinoma where the presence of two separated left hepatic arteries permitted to deliver sequentially high-dose ^{90}Yttrium to the tumor and lower dose to future resected liver, allowing uneventful left hepatectomy 3 mo later. This observation suggests that, when different arterial accesses exist to tumor and future resected non-tumor liver, sequential radioembolization with different radiation doses could represent a new preoperative strategy, optimizing the tumoricidal effect while minimizing the risk of radiation-induced liver damage.

Vouche M, Degrez T, Bouazza F, Delatte P, Gomez Galdon M, Hendlisz A, Flamen P, Donckier V. Sequential tumor-directed and lobar radioembolization before major hepatectomy for hepatocellular carcinoma. *World J Hepatol* 2017; 9(36): 1372-1377 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i36/1372.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i36.1372

INTRODUCTION

Partial hepatectomy (PH) and tumor destruction with radiofrequency (RF) are the first therapeutic options in patients with hepatocellular carcinoma (HCC) and compensated cirrhosis who are not candidates for liver transplantation (LT)[1,2]. However, the feasibility and efficacy of these treatments are dramatically limited by underlying liver disease and high tumor recurrence rates. At the present time, no neoadjuvant treatment has been validated for improving the safety and efficacy of PH and RF in this setting. In particular, locoregional treatment with transarterial chemoembolization (TACE) has failed to demonstrate significant long-term benefits when used before PH or RF for HCC[3-5]. Furthermore, when a major resection of 3 or more segments is indicated in cirrhotic livers, preoperative homolateral portal vein embolization (PVE) is recommended to induce an atrophy of the future resected liver and a compensatory hypertrophy of the future liver remnant (FLR)[6,7]. This strategy, however, leaves the tumor untreated while waiting for liver regeneration, exposing the patient to the risk of tumor progression before the surgery[8].

Selective internal radiotherapy (SIRT), relying on the transarterial embolization of ^{90}yttrium-loaded microspheres (^{90}Y), has become a new tool for treatment of liver tumors. In HCC, SIRT has been demonstrated to improve survival in patients who are not candidates for curative-intent therapies and to allow tumor control while waiting for LT[9-13]. Furthermore, SIRT can be used preoperatively and the feasibility and safety of post-SIRT surgery has been now assessed[14-17]. The tumoricidal effect of SIRT, leading to tumor downsizing, may significantly modify the extent of surgery or allow the resection of initially unresectable tumors. Moreover, regional intra-arterial hepatic embolization with ^{90}Y could also induce the atrophy of the embolized segments and a compensatory hypertrophy of the non-embolized liver[18,19]. This specificity allows for the design of new therapeutic strategies, integrating neoadjuvant SIRT into current surgical approaches to liver tumors, particularly for HCC in cirrhotic patients.

We describe here the case of a patient with centrally-located HCC, treated with sequential intra-tumor and left lobar ^{90}Y embolization before a left hepatectomy. This case illustrates the new possibilities offered by the use of SIRT as a preoperative therapy before major liver resection for HCC in cirrhotic patients.

CASE REPORT

A 70-year-old man with a past history of alcohol consumption presented with a liver tumor. Contrast-enhanced magnetic resonance imaging (MRI) demonstrated a 40 mm mass in segment IV with vascular characteristics of HCC (arterial wash-in and portal wash-out) and features of cirrhosis (Figure 1A and B). Blood tests, including liver function and alpha-fetoprotein, were normal and the patient was classified as Child-Pugh A, with a MELD score of 7. Complete work-up did not demonstrate extra-hepatic metastasis. Accordingly, the tumor corresponded to Okuda stage 1 and BCLC stage A. Due to the patient's age, the comorbidities, and the patient's preferences, LT was not recommended during multidisciplinary meeting. Therefore, a left hepatectomy (resection of segments II-III-IV) was proposed and, due to the presence of cirrhosis, preoperative treatment to modulate FLR volume and function was indicated. Analysis of liver volumes on angio-CT scan showed a total liver volume (TLV) of 2339 mL, a tumor volume of 36 mL, a left liver volume (segments II, III, IV) of 812 mL, and an FLR volume (segments I, V, VI, VII, VIII) of 1527 mL, corresponding to a FLR/TLV of 65% and an FLR/body weight ratio of 0.68. On the basis of our previous experience[20] and in relation to the proximity of the tumor to the portal bifurcation that might

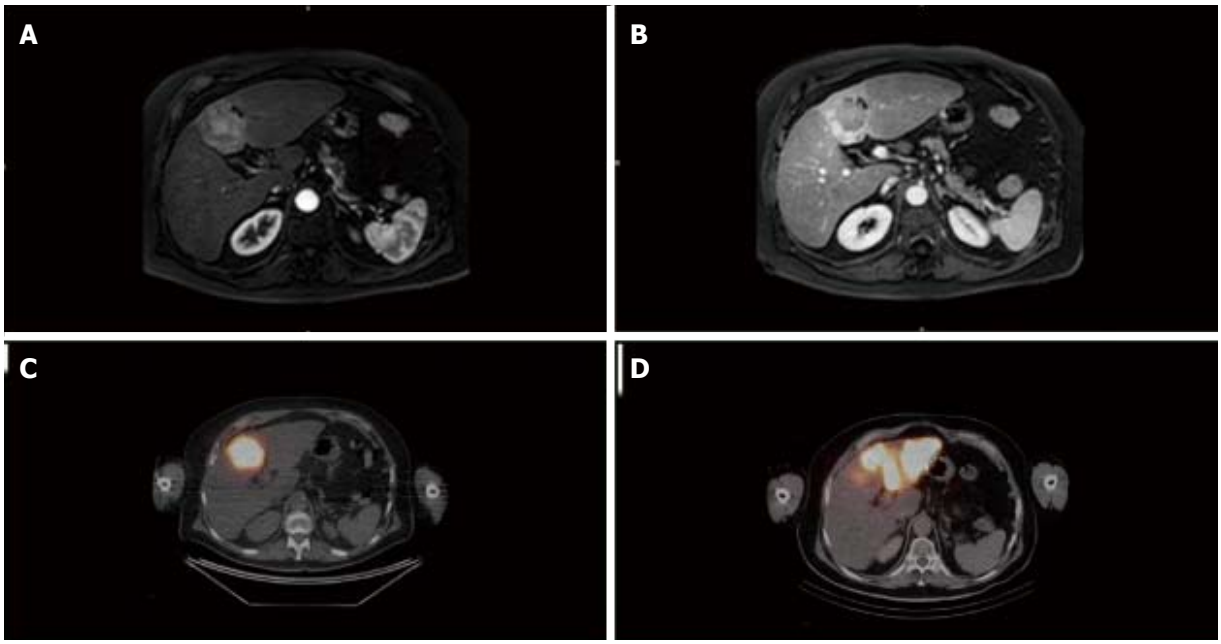

Figure 1 Preoperative imaging. A and B: Baseline contrast-enhanced magnetic resonance imaging (MRI). Contrast-enhanced MRI demonstrated a 40 mm mass in segment IV of the liver with arterial wash-in (A) and wash-out on the portal venous phase (B) and features of cirrhosis (irregular surface, relative hypertrophy of segment I); C and D: Selective intra-tumor deposition of 90Y microspheres after first SIRT session (C) and deposition of 90Y microspheres to segments II and III after the second SIRT session (D).

preclude the chance for resection in case of progression, SIRT was preferred to PVE as preoperative treatment.

Simulation of SIRT with ^{99}Tc macroaggregated albumin showed no extra-hepatic deposition and excellent tumor targeting. In addition, the angiography demonstrated a variant hepatic arterial anatomy characterized by a left hepatic artery arising from the right gastric artery, a segment IV artery arising from the gastroduodenal artery and a right hepatic artery arising normally from the celiac trunk. Therefore, 2-step SIRT using different ^{90}Y doses was decided upon in order to maximize the dose of ^{90}Y selectively delivered to the tumor and to minimize the potential toxicity related to intense radioembolization of a large liver volume. First, ^{90}Y hyperselective radioembolization of the segment IV artery to the tumor was performed, allowing the delivery 161 Gy to segment Ⅳ (Figure 1C). No side effects related to this procedure were observed. Twenty-eight days later, the left hepatic artery was catheterized and ^{90}Y microspheres injected, allowing for the delivery of 120 Gy to segments II and III (Figure 1D). No side effects were observed following this procedure. At day 110 after the second SIRT, contrast-enhanced MRI showed a significant tumor response (size reduction of the tumor diameter from 40 to 34 mm and complete necrosis on arterial phase) (Figure 1D). On the same examination, segments Ⅱ, Ⅲ, and Ⅳ measured 545 mL, corresponding to a 34% reduction, and FLR measured 1643 mL, corresponding to a minimal increase of 2%. At day 115 after the second SIRT, a left hepatectomy, partially extended to segment Ⅴ, was performed. Operative exploration confirmed the cirrhosis while the entire left lobe appeared as atrophic and fibrotic (Figure 2A). The surgery proceeded uneventfully. Intraoperative blood losses were 800 mL and no blood transfusions were required. Postoperative course was unremarkable clinically and biologically (minimal values of PT, peak INR, and total bilirubin respectively of 56%, 1.3, and 1.5 mg/dL on day 3 after surgery) and the patient was discharged on day 14. On macroscopic examination of the operative specimen, small foci of cancer cells < 5 mm were observed within a tumor necrotic/fibrotic zone of 55 mm in diameter (Figure 2b). Pathological examination demonstrated a margin-free resection and a major tumor response as indicated by approximately less than 10% of residual cancer cells (Figure 2C and D).

DISCUSSION

PH remains the treatment of choice in patients with large HCC and compensated cirrhosis without significant portal hypertension and who are not candidates for LT[1]. When a major resection is required, preoperative PVE to adapt the FLR is currently considered as the standard procedure. The present case illustrates that neoadjuvant SIRT before surgery may represent now an alternative to this classical sequence. The rationale for considering the use of SIRT before PH for HCC in cirrhotic patients relies on several factors. The first is that SIRT is an effective local treatment for HCC[13]. Thus, if liver surgery would ultimately be found to be infeasible, the patient would still receive an efficient anti-tumor therapy. Secondly, when ^{90}Y microspheres are administered both selectively in the tumor and

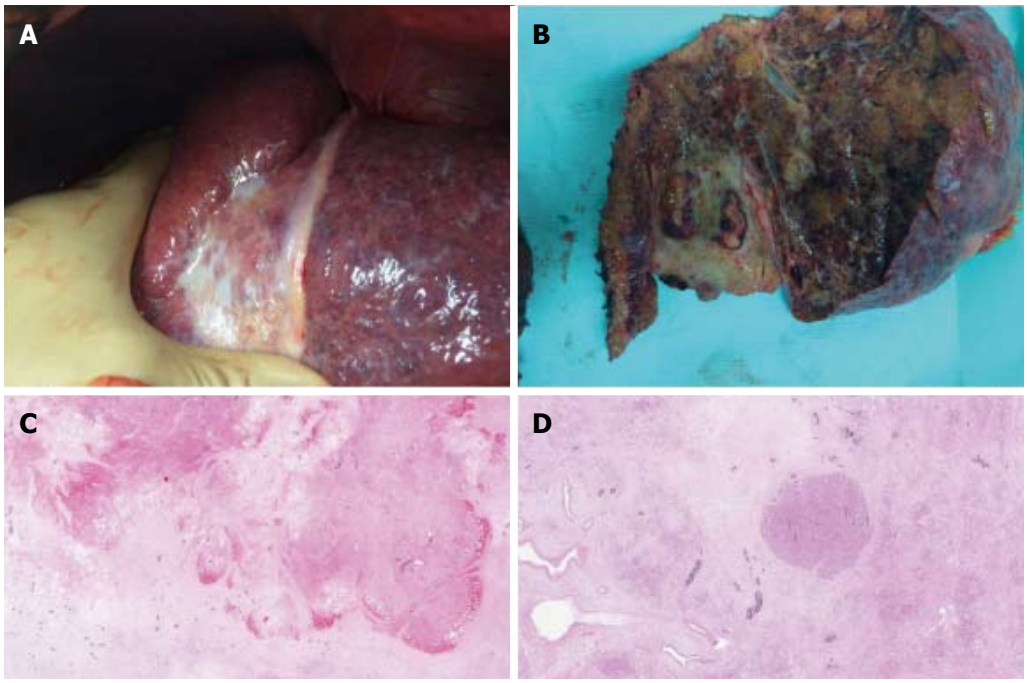

Figure 2 Intra- and postoperative images. A: Intraoperative view showing the cirrhosis and the post-selective internal radiotherapy (SIRT) relative atrophy of the left liver; B: Resected specimen showing small residual cancer cells foci with the necrotic and fibrotic zone targeted by segment IV high-dose SIRT; C: Pathological view showing massive necrosis and fibrosis together with the presence of microspheres; D: Pathological view showing a residual hepatocellular carcinoma focus, surrounded by necrosis and fibrosis together with the presence of microspheres.

regionally in the future resected liver segments (radiation lobectomy), SIRT has the unique capacity to induce an effective tumoricidal effect together with the atrophy of the future resected liver and a compensatory hypertrophy of the FLR. As compared with preoperative PVE, this may reduce the risk of tumor progression while waiting for functional and volumetric adaptation of the FLR. Finally, and as described for TACE[21], response to SIRT may potentially serve as a predictive factor both for the safety and the efficacy of the surgery. The feasibility of major liver resection after ^{90}Y radiation lobectomy has been assessed. However, particularly in cirrhotic livers, such large liver volume irradiation exposes the patient to the risk of radiation-induced liver disease (RILD)[22]. In the present case, the hepatic arterial anatomy allowed to perform a 2-step SIRT, delivering first high ^{90}Y dose to the segment Ⅳ tumor, followed by an ablative but safe irradiation dose to left lobe (segments Ⅱ and Ⅲ). As a dose-tumor response correlation was demonstrated over 170 Gy[23] and FLR volume modulation was found for doses approximating 120 Gy[18], such sequential procedures may potentially optimize the neoadjuvant effect of the treatment while reducing the toxicity and the risk of RILD. At 3 mo after SIRT, we observed volumetric effects within the embolized regions, as indicated by significant tumor shrinking and left lobe atrophy. In contrast, virtually no increase of the non-embolized FLR was detected, potentially related to the relatively short time period between SIRT and surgery[18]. Despite the absence of significant volumetric regeneration of the right liver, no sign of liver insufficiency has been observed after the left hepatectomy, potentially in relation with favorable initial FLR/TLV ratio. Finally, this case indicates that, despite the so-called ablative ^{90}Y dose given to the tumor, a complete pathological response was not obtained, highlighting the need to still resect these irradiated tumors whenever possible.

In conclusion, when distinct arteries to the tumor and to the future resected liver can be selectively catheterized, sequential ^{90}Y embolization with modulated doses to the tumor and to the future resected liver could represent a new strategy for improving the safety and the efficacy of neoadjuvant radioembolization before major liver resection in cirrhotic patients. The potential oncological benefit of this therapeutic combination remains to be evaluated.

ARTICLE HIGHLIGHTS

Case characteristics

A seventy years old patient presented with a segment Ⅳ liver tumor.

Clinical diagnosis

Due to the presence of alcohol-related cirrhosis, a diagnosis of hepatocellular carcinoma was suspected.

Differential diagnosis

Differential diagnosis included other solid liver tumors, primary or secondary.

Laboratory diagnosis

Laboratory data, including alpha-fetoprotein were not contributive.

Imaging diagnosis

Contrast-enhanced magnetic resonance imaging demonstrated a 40 mm mass in segment Ⅳ of the liver with vascular characteristics of hepatocellular carcinoma, such as arterial phase wash-in and portal phase wash-out and features of cirrhosis. Angiography demonstrated two separated left hepatic arteries, for segment Ⅳ and for segments Ⅱ and Ⅲ, allowing selective access to the tumor and to the future resected liver.

Pathological diagnosis

On operative specimen, pathology confirmed the diagnosis of hepatocellular carcinoma and a major response to preoperative radioembolization as indicated by less than 10% residual cancer cells.

Treatment

Left hepatectomy was preceded by sequential radioembolizations, delivering high-dose radiation to the tumor and then, lower dose to the future resected liver. This 2-steps approach aimed to maximize tumoricidal effect while limiting the risks for radiation-induced liver disease and liver insufficiency.

Related reports

In such cases of hepatocellular carcinoma requiring a major hepatectomy in patients with compensated cirrhosis, resectability is dramatically limited by the risk of postoperative liver insufficiency.

Experiences and lessons

This case indicates that, when arterial anatomy allows it, sequential radioembolizations with different radiation doses to the tumor and to the future resected liver could represent a new strategy to maximize the tumoricidal effect while preserving the atrophic effect but reducing the risk of radiation-induced liver injury.

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CASE REPORT

Primary biliary cholangitis metachronously complicated with combined hepatocellular carcinoma-cholangiocellular carcinoma and hepatocellular carcinoma

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Author contributions: Ide R and Oshita A made conception and design of this case report; authors other than Ide R and Oshita A, Nishisaka T, Nakahara H, Aimitsu S and Itamoto T contributed to collection and interpretation of data; Ide R and Oshita A wrote the draft manuscript, and other authors performed critical revision of the manuscript; all authors gave final approval of the version to be published; Oshita A has overall responsibility and guarantees the scientific integrity.

Informed consent statement: The patient provided informed consent for the publication of this manuscript and accompanying images.

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Abstract

Primary biliary cholangitis (PBC) is a progressive cholestatic liver disease characterized by the presence of highly specific antimitochondrial antibodies, portal inflammation and lymphocyte-dominated destruction of the intrahepatic bile ducts, which leads to cirrhosis. While its pathogenesis remains unclear, PBC that shows histological progression to fibrosis carries a high risk of carcinogenesis; the same is true of viral liver diseases. In patients with PBC, the development of hepatocellular carcinoma (HCC) is rare; the development of combined hepatocellular carcinoma and cholangiocellular carcinoma (cHCC-CCC) is extraordinary. Herein, we report a rare case of PBC metachronously complicated by cHCC-

CCC and HCC, which, to the best of our knowledge, has never been reported. We present a case report of a 74-year-old Japanese woman who was diagnosed as PBC in her 40's by using blood tests and was admitted to our department for further management of an asymptomatic liver mass. She had a tumor of 15 mm in size in segment 8 of the liver and underwent a partial resection of the liver. Subsequent pathological findings resulted in the diagnosis of cHCC-CCC, arising from stage 3 PBC. One year after the initial hepatectomy, a second tumor of 10 mm in diameter was found in segment 5 of the liver; a partial resection of the liver was performed. Subsequent pathological findings led to HCC diagnosis. The component of HCC in the initial tumor displayed a trabecular growth pattern while the second HCC showed a pseudoglandular growth pattern, suggesting that metachronous tumors that arise from PBC are multicentric.

Key words: Primary biliary cholangitis; Combined hepatocellular carcinoma and cholangiocellular carcinoma; Hepatocellular carcinoma

Core tip: Primary biliary cholangitis (PBC) is a progressive cholestatic liver disease characterized by the presence of highly specific antimitochondrial antibodies, portal inflammation and lymphocyte-dominated destruction of the intrahepatic bile ducts, which leads to cirrhosis. While its pathogenesis remains unclear, PBC that shows histological progression to fibrosis carries a high risk of carcinogenesis; the same is true of viral liver diseases. In patients with PBC, the development of hepatocellular carcinoma is rare; the development of combined hepatocellular carcinoma and cholangiocellular carcinoma (cHCC-CCC) is extraordinary. Herein, we report a rare case of PBC metachronously complicated by cHCC-CCC and HCC, which, to the best of our knowledge, has never been reported.

Ide R, Oshita A, Nishisaka T, Nakahara H, Aimitsu S, Itamoto T. Primary biliary cholangitis metachronously complicated with combined hepatocellular carcinoma-cholangiocellular carcinoma and hepatocellular carcinoma. *World J Hepatol* 2017; 9(36): 1378-1384 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i36/1378.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i36.1378

INTRODUCTION

Primary biliary cholangitis (PBC)[1] is a progressive cholestatic liver disease characterized by the presence of a highly specific antimitochondrial antibody, portal inflammation, and lymphocyte-dominated destruction of the intralobular bile ducts, which lead to cirrhosis. According to recent and relatively large cohort studies conducted in European countries, the United States and Japan, the development of hepatocellular carcinoma (HCC) is estimated to be 0.7%-3.6%; this frequency increases as histological stages progress[2]. While its pathogenesis remains unclear, PBC cases that display histological progression to fibrosis are at a high risk of carcinogenesis; the same is true of viral liver diseases[3,4]. Although some cases of PBC complicated by HCC have been reported[5-8], to our knowledge, a case of PBC with cholangiocellular carcinoma (CCC) has never been described. In patients with PBC, the development of combined hepatocellular carcinoma and cholangio cellular carcinoma (cHCC-CCC) is extremely rare[9]. Herein, we report a case of PBC metachronously complicated by cHCC-CCC and HCC.

CASE REPORT

A 74-year-old Japanese woman was diagnosed as PBC in her 40's by using blood tests. Imaging studies, including abdominal ultrasonography (US) and computed tomography (CT), and tumor markers consisting of alpha fetoprotein (AFP) and protein induced by vitamin K absence (PIVKA-II) were checked up every 6 mo to 12 mo[4]. She was admitted to our department for further management of an asymptomatic liver mass. The patient denied alcohol consumption. Hepatitis B virus antigen and anti-hepatitis C virus antibody tests were negative. Liver function test results, with daily intake of 600 mg of ursodeoxycholic acid, were stable. Serum levels of AFP, PIVKA-II, carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9 and the L3 fraction of AFP were all within normal limits (Table 1).

Abdominal US, dynamic CT, and magnetic resonance imaging (MRI) showed a liver tumor of 15 mm in size in segment 8 of the liver. Since the tumor was located in the peripheral lesion and was in contact with the middle hepatic vein (MHV), we performed partial resection of the liver in segment 8 including partial resection of MHV. Hematoxylin-eosin (HE) staining revealed two components consisting of the trabecular type of HCC and CCC, resulting in the definitive diagnosis of cHCC-CCC. According to the classification for the severity of PBC[10,11], the hepatic parenchyma, excluding carcinomatous tissue, showed stage 3 PBC (Figure 1). In the immunohistochemistry, the component of HCC was negative for AFP but positive for cytokeratin (CK) 18 and hepatocyte, while that of CCC was positive for CK7 and CK19. The components of both HCC and CCC are positive for the epithelial cell adhesion molecule (EpCAM) (Figure 2).

One year after the initial hepatectomy, tumor marker levels for AFP, PIVKA-II, CEA and CA 19-9 were within normal limits; only AFP-L3 isoform level was elevated (Table 2). Dynamic CT and MRI showed a peripheral tumor of 10 mm in diameter in segment

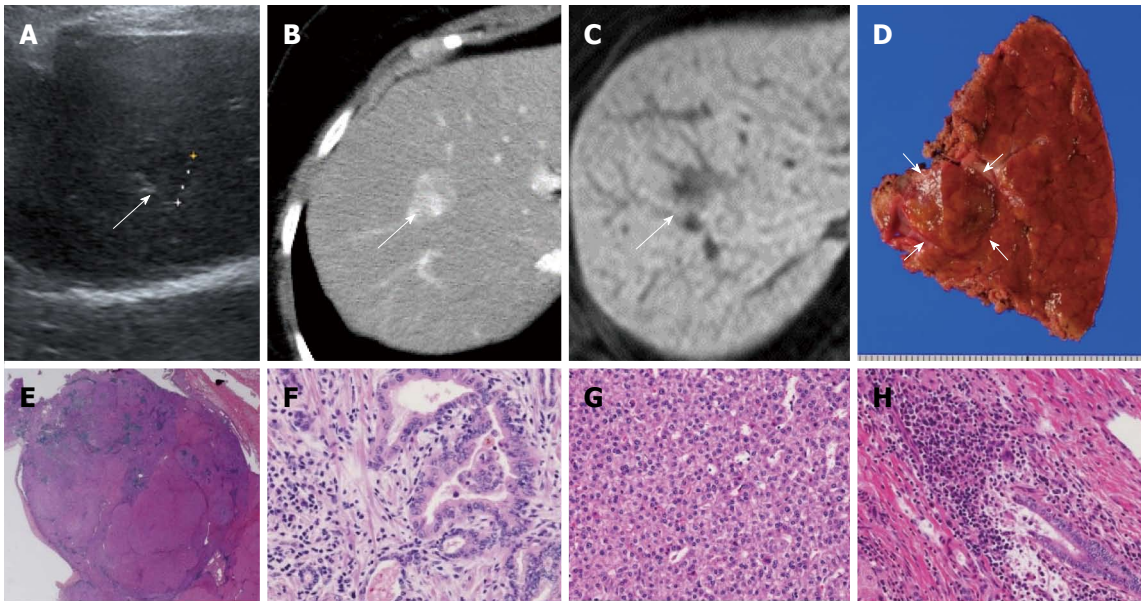

Figure 1 The initial tumor. A: Low-echoic tumor of 15 mm in size in segment 8 in US; B: The enhanced tumor on the early phase in dynamic CT; C: Low-intensity tumor on the hepatocyte phase in MRI; D: Cut surface of the 15-mm solid mass in segment 8; E: HE staining of the resected specimen; F: Adenocarcinoma in the component of CCC; G: HCC with a trabecular pattern; H: Dense fibrous tissue was formed and intrahepatic biliary ducts were showing destruction, while a loose lymphoid aggregate indicated stage 3 of primary biliary cirrhosis. CCC: Cholangiocellular carcinoma; CT: Computed tomography; HCC: Hepatocellular carcinoma; HE: Hematoxylin-eosin; MRI: Magnetic resonance imaging; US: Ultrasonography.

Table 1 Laboratory data on the initial hepatectomy

WBC	5800/μL	ALP	228 U/L	PIVKA-II	18 mAU/mL
RBC	432 × 10^4/μL	γ-GTP	65 U/L	AFP	3 ng/mL
Hb	13.0 g/dL	ChE	280 IU/L	AFP-L3	0.5%
Ht	38%	BUN	14.5 mg/dL	CEA	1.2 ng/mL
Plt	22.6 × 10^4/μL	Cr	0.54 mg/dL	CA 19-9	7 U/mL
PT	77.3%	T-Chol	203 mg/dL	ANA	× 40
PT-INR	1.04	TG	77 mg/dL	AMA	× 640
TP	7.9 g/dL	ICG-R15	8.3%	AMA-M2	158 Index
Alb	4.2 g/dL	Glucose	109 mg/dL	HBs Ag	(-)
TBil	0.5 mg/dL	CRP	0.2 mg/dL	HBs Ab	(-)
AST	19 U/L	IgG	1760 mg/dL	HBc Ab	(-)
ALT	14 U/L	IgM	305 mg/dL	HCV Ab	(-)
LDH	183 U/L				

AFP: Alpha-fetoprotein; AFP-L3: A Lens culinaris agglutinin-reactive fraction of alpha-fetoprotein; Alb: Albumin; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AMA: Antimitochondrial antibody; AMA-M2: Anti-mitochondrial M2 antibody; ANA: Antinuclear antibodies; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CA 19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; ChE: Cholinesterase; Cr: Creatinine; CRP: C-reactive protein; γ-GTP: Gamma-glutamyltransferase; Hb: Hemoglobin; HBcAb: Hepatitis B core antibody; HBsAb: Hepatitis B surface antibody; HBsAg: Hepatitis B virus antigen; HCVAb: Hepatitis C virus antibody; Ht: Hematocrit; ICG-R15: 15-min retention rates of indocyanine green test; IgG: Immune globulin G; IgM: Immune globulin M; LDH: Lactate dehydrogenase; PIVKA-II: Prothrombin-induced vitamin K absence II; Plt: Platelet; PT: Prothrombin time; PT-INR: Prothrombin time international normalized ratio; RBC: Red blood cell count; TBil: Total bilirubin; T-Chol: Total cholesterol; TG: Triglyceride; TP: Total protein; WBC: White blood cell count.

5 of the liver. Since it was not possible to detect the tumor with intraoperative US, partial resection of the liver on the basis of the anatomical structure, including the Glissonean sheath and the hepatic vein, was performed. HE staining revealed a pseudoglandular pattern of HCC (Figure 3). In the immunohistochemistry, recurrent HCC was negative for AFP and EpCAM but positive for CK18 and hepatocyte (data not shown). There was no recurrence and/or metastasis 10 mo after re-hepatectomy.

DISCUSSION

While some cases of PBC complicated by HCC have been reported[5-8], only 1 case of PBC with cHCC-CCC has been reported[9]. The present case of PBC was metachronously complicated by both cHCC-CCC and HCC; to the best of our knowledge, such a case has never been reported.

While the etiology of PBC remains unknown, it is well known that the intrahepatic bile ducts are to be destructed slowly and progressively, leading to cirrhosis[12]. PBC

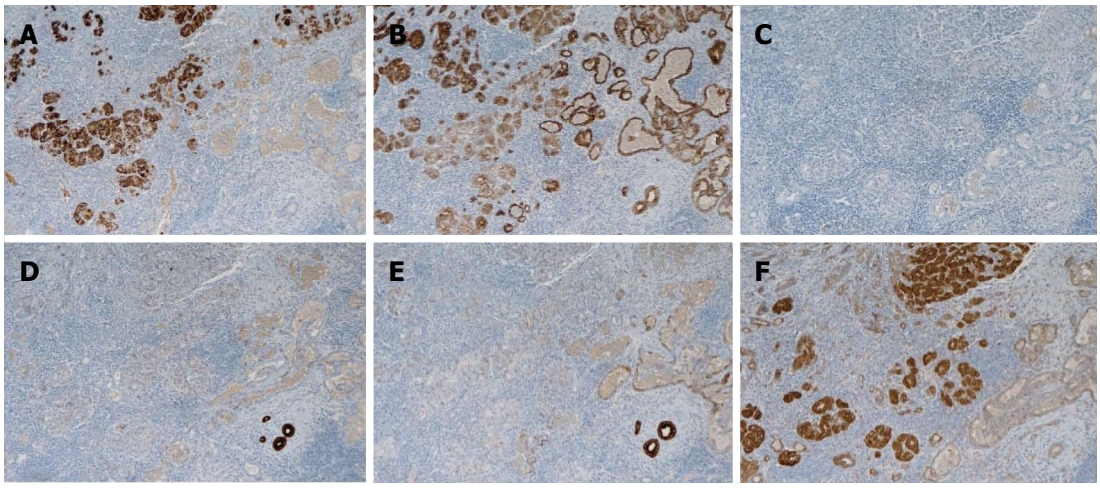

Figure 2 Immunohistochemistry findings for the initial tumor. A: HCC component stained positive for hepatocyte; B: HCC component stained positive for CK18; C: Both HCC and CCC components stained negative for alpha fetoprotein; D: CCC component stained positive for CK7; E: CCC component stained positive for CK19; F: Epithelial cell adhesion molecule stained positive for the HCC component and weakly positive for the CCC component. CCC: Cholangiocellular carcinoma; CK: Cytokeratin; HCC: Hepatocellular carcinoma.

Table 2 Laboratory data on the re-hepatectomy

WBC	3600/μL	AST	29 U/L	PIVKA-II	28 mAU/mL
RBC	397 × 10^4/μL	ALT	18 U/L	AFP	5 ng/mL
Hb	12.0 g/dL	LDH	186 U/L	AFP-L3	11.7%
Ht	35.9%	ALP	300 U/L	CEA	1.0 ng/mL
Plt	22.3 × 10^4/μL	γ-GTP	79 U/L	CA 19-9	29 U/mL
PT	77.3%	ChE	211 IU/L	ICG-R15	7.4%
PT-INR	1.12	BUN	16.1 mg/dL	Glucose	138 mg/dL
TP	7.3 g/dL	Cr	0.6 mg/dL	CRP	0.2 mg/dL
Alb	3.8 g/dL	T-Bil	0.4 mg/dL		

AFP: Alpha-fetoprotein; AFP-L3: A Lens culinaris agglutinin-reactive fraction of alpha-fetoprotein; Alb: Albumin; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CA19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; ChE: Cholinesterase; Cr: Creatinine; CRP: C-reactive protein; γ-GTP: Gamma-glutamyltransferase; Hb: Hemoglobin; Ht: Hematocrit; ICG-R15: 15-min retention rates of indocyanine green test; LDH: Lactate dehydrogenase; PIVKA-II: Prothrombin-induced vitamin K absence II; Plt: Platelet; PT: Prothrombin time; PT-INR: Prothrombin time international normalized ratio; RBC: Red blood cell count; T.Bil: Total bilirubin; TP: Total protein; WBC: White blood cell count.

occurs more often in middle-aged women and is often asymptomatic in its early stage[13,14]. The frequency of HCC development in patients with PBC is estimated to be 0.7%-3.6%. While this frequency increases as the histological stages progress[2,5,6,9,11,15-20], the carcinogenic mechanism of primary liver cancer in PBC remains unclear. Although our patient's PBC progressed to stage 3 of 4, when primary liver cancer was found, she had no liver cirrhosis symptoms.

Few studies have evaluated the imaging characteristics of cHCC-CCC, and no studies have evaluated the ability of preoperative imaging to determine diagnosis. The appearance of HCC and CCC is well known on contrast-enhanced MRI and CT. The histological composition and relative ratio of CCC and HCC components within cHCC-CCC appear to dictate the imaging appearance. Tumors may show features typical of HCC, such as arterial enhancement, washout and pseudocapsule, whereas other regions within the tumor show progressive or delayed enhancement, necrosis and possible ductal dilation more akin to CCC[21]. The cHCC-CCC display enhancement patterns resembling CCC or HCC in comparable proportion on both contrast-enhanced US and CT[22]. Some suggest that the combination of imaging features and tumor markers may be helpful in preoperative diagnosis of cHCC-CCC[23]. In our case, since dynamic CT showed arterial enhancement and washout imaging, we performed initial hepatectomy expected for HCC.

Allen *et al*[24] classified cHCC-CCC into three subtypes: type A, "double cancer" representing cases in which HCC and CCC exist separately; type B, "combined" type, HCC and CCC components existing contiguously, but independently; and type C, "mixed" type, consisting of truly combined HCC and CCC components originating from the same tumor. Based on the morphological findings from HE staining, the present case was classified as mixed type cHCC-CCC.

In recent years, the ability of hepatic precursor cells to differentiate into hepatocytes and bile duct cells,

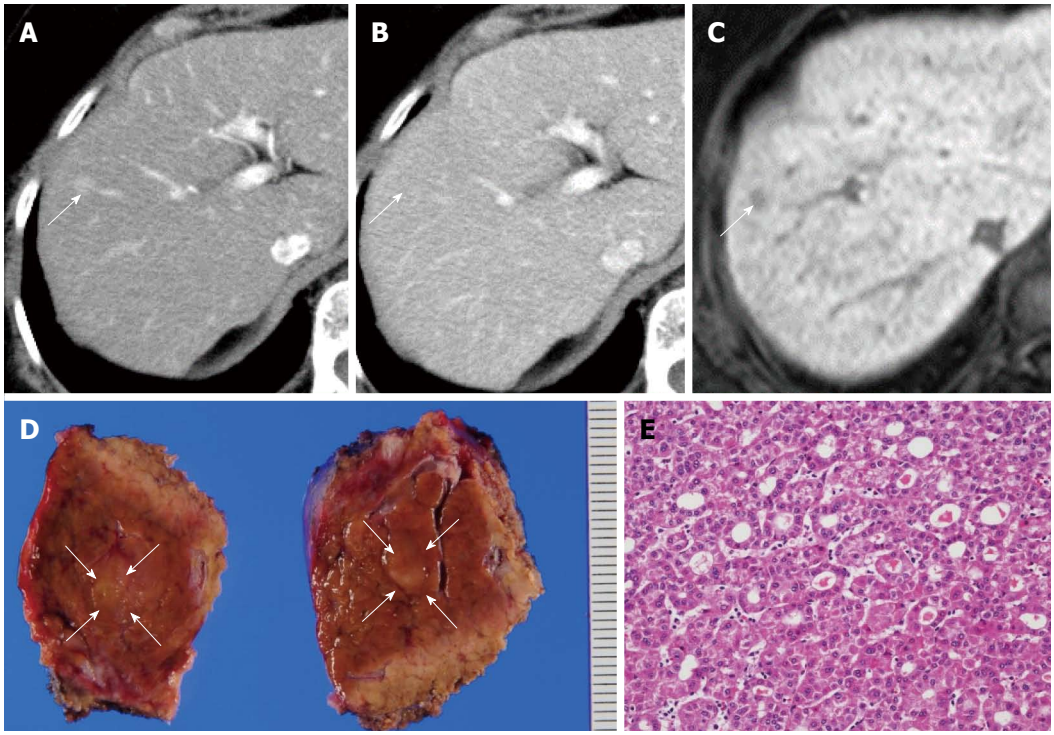

Figure 3 The second tumor. A: The enhanced tumor of 10 mm in diameter in segment 5 on the early phase in dynamic CT; B: The iso-density tumor on the delayed phase; C: Low intensity tumor on the hepatocyte phase in MRI; D: Cut surface of the 10-mm solid mass in segment 5; E: HE staining showing a pseudoglandular pattern of HCC. CT: Computed tomography; HCC: Hepatocellular carcinoma; HE: Hematoxylin-eosin; MRI: Magnetic resonance imaging.

and of hepatic stem cells to proliferate and differentiate have been proposed. As candidate stem cells, cells derived from the Herring duct or small oval cells may be able to differentiate into hepatocytes and bile duct cells[25-27]. Carcinogenesis of the precursor cells has been suggested as a developmental mechanism for cHCC-CCC with tissue components of HCC and CCC. In the present case, as Theise *et al*[28] indicated, the result of EpCAM immunohistochemistry (a stem cell marker), might be consistent with that of mixed type cHCC-CCC.

The pathological results of the initial tumor showed the trabecular pattern in the component of HCC, while that of the second tumor showed the pseudoglandular pattern in HCC. Immunohistochemistry also revealed the different pattern, which led the authors to speculate that the second tumor did not recur from the HCC component of cHCC-CCC, but the multicentric development of PBC-derived metachronous tumors.

In conclusion, we herein report a rare case of PBC metachronously complicated by both cHCC-CCC and HCC. In patients with PBC, it is necessary to check up not only liver function but also carcinogeneses, including HCC, CCC and cHCC-CCC.

ARTICLE HIGHLIGHTS

Case characteristics

A 74-year-old Japanese woman was diagnosed as primary biliary cholangitis (PBC) in her 40's by using blood tests. Imaging studies, including abdominal ultrasonography (US) and computed tomography (CT), and tumor markers consisting of alpha fetoprotein (AFP) and protein induced by vitamin K absence (PIVKA-II) were checked up every 6-12 mo. She was admitted to the authors' department for further management of an asymptomatic liver mass.

Differential diagnosis

Combined hepatocellular carcinoma and cholangiocellular carcinoma (cHCC-CCC), hepatocellular carcinoma (HCC) and cholangiocellular carcinoma (CCC) were considered from imaging tests.

Laboratory diagnosis

In the initial surgery, serum levels of AFP, PIVKA-II, carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9, and the L3 fraction of AFP were all within normal limits. One year after the initial hepatectomy, tumor marker levels for AFP, PIVKA-II, CEA, and CA 19-9 were within normal limits; only AFP-L3 isoform level was elevated.

Imaging diagnosis

The authors diagnosed both the first and second tumors as HCC from the imaging findings.

Pathological diagnosis

First, hematoxylin-eosin (HE) staining revealed two components, consisting of the trabecular type of HCC and CCC, resulting in the definitive diagnosis of cHCC-CCC. Second, HE staining revealed a pseudoglandular pattern of HCC.

Treatment

The first one was that the tumor was involved in middle hepatic vein (MHV). If radiofrequency ablation was performed, the cooling effect around the MHV would have occurred, leading to the insufficient ablation. The second one was that the tumor was not detected using US preoperatively. Moreover, the tumor was not detected even with intraoperative contrast-enhanced US. Therefore,

the authors performed partial resection on the basis of the anatomical structure, including the Glissonean sheath and the hepatic vein.

Related reports

This report relates to this reference: Kobayashi M, Furuta K, Kitamura H, Oguchi K, Arai M, Koike S, Nakazawa K. A case of primary biliary cirrhosis that complicated with combined hepatocellular and cholangiocellular carcinoma. *Clin J Gastroenterol* 2011; 4: 236-241.

Term explanation

PBC: Primary biliary cholangitis, is marked by slow progressive destruction of the intrahepatic bile ducts, which leads to cirrhosis.

Experiences and lessons

In patients with PBC, it is necessary to check up not only liver function but also carcinogenesis including HCC, CCC and cHCC-CCC.

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CASE REPORT

Eosinophilic cholangitis treatment with budesonide

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Author contributions: De Roza MA and Lim CH designed the report and analyzed the data; Lim CH reported and monitored outcomes; De Roza MA wrote the report; Both De Roza MA and Lim CH made critical revisions before final approval of the report.

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Abstract

Eosinophilic cholangitis is a rare cause of deranged obstructive liver function tests. It has been described as a great mimicker for malignant biliary strictures and bile duct obstruction. There are only case reports available on treatment experience for eosinophilic cholangitis. A large proportion of patients present with biliary strictures for which they have undergone surgery or endoscopic treatment and a small proportion was given systemic corticosteroid. We share our treatment experience using budesonide which has fewer systemic side effects to prednisolone and avoids invasive management.

Key words: Eosinophilic cholangitis; Budesonide; Biliary stricture; Eosinophilia; Obstructive liver function test

Core tip: Eosinophilic cholangitis is a rare cause of obstructive liver function tests and secondary sclerosing cholangitis. Peripheral eosinophilia is the most useful laboratory hint for the diagnosis thus avoiding invasive endoscopic or surgical treatment. It is normally treated with a prolonged duration of corticosteroids, risking the development of corticosteroid adverse effects. We describe our successful experience with budesonide, an alternative treatment option which has a higher first pass effect resulting in fewer systemic side effects.

De Roza MA, Lim CH. Eosinophilic cholangitis treatment with budesonide. *World J Hepatol* 2017; 9(36): 1385-1388 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i36/1385.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i36.1385

INTRODUCTION

Eosinophilic cholangitis is a rare cause of obstructive liver function tests. It has been described as a great mimicker for malignant biliary strictures and bile duct obstruction. There are only case reports available on treatment experience for eosinophilic cholangitis. A large proportion of patients present with biliary strictures for which they

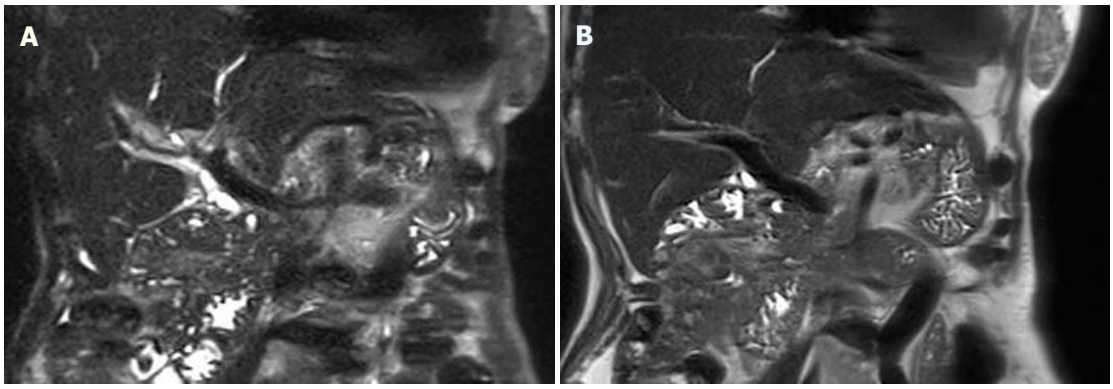

Figure 1 T2 magnetic resonance imaging. A: T2 magnetic resonance imaging segment Ⅷ biliary stricture before treatment; B: T2 magnetic resonance imaging after budesonide showing resolution of segment Ⅷ stricture.

have undergone surgery or endoscopic treatment. A smaller proportion was given corticosteroid treatment and most involved the use of systemic corticosteroids such as prednisolone.

CASE REPORT

Our patient is a 75-year-old Chinese retired lady. She does not smoke, consume alcohol or substances. Past medical history of note is hypertension and septic arthritis with a right first metatarsal osteomyelitis for which she underwent a Ray's amputation and was discharged to a step-down facility for slow stream rehabilitation.

She presented with deranged liver function tests (LFT), done during routine follow up at her rehabilitation centre. She was otherwise asymptomatic with no abdominal pain, fever, nausea, vomiting or diarrhoea. She did not take any supplements or over the counter medications. She was prescribed two weeks of antibiotics (one week of cefazolin followed by one week of oral Augmentin) for osteomyelitis which was treated with ray's amputation. However, her antibiotic course was completed almost 2 mo prior to presentation.

Her baseline LFT (taken during admission for osteomyelitis) was unremarkable except for a mildly raised Alkaline Phosphatase which we attributed to her bone infection. Her baseline LFT was as such: Albumin 38 g/L (normal range 40-51 g/L), bilirubin 11 μmol/L (normal range 7-32 μmol/L), alkaline phosphatase (ALP) 126 U/L (normal range 39-99 U/L), alanine aminotransferase (ALT) 14 U/L (normal range 6-66 U/L), aspartate aminotransferase (AST) 24 U/L (normal range 6-66 U/L).

She was referred to us 2 mo later with a predominantly cholestatic LFT and eosinophilia with markedly raised serum IgE levels. Her test results are as follows: Albumin 34 g/L, (normal range 40-51 g/L), bilirubin 20 μmol/L, (normal range 7-32 μmol/L), ALP 803 U/L, (normal range 39-99 U/L), ALT 234 U/L, (normal range 6-66 U/L), AST 145 U/L, (normal range 6-66 U/L), GGT 667 U/L (normal range 14-94 U/L), total leukocyte count 7.75 × 10^9/L (normal range 4.0-10.0^9/L), eosinophils 23.1% (normal range 0-6%), eosinophil absolute count 1.79 × 10^9/L (normal range 0.04-0.44 × 10^9/L), IgG, serum 12.08 g/L (normal range 5.49-17.11 g/L), IgA, serum 2.54 g/L (normal range 0.47-3.59 g/L), IgE, serum 1064 IU/ml (normal range 18-100 IU/mL).

Anti-MPO, Anti-PR3, Antinuclear Antibody, Anti Liver Antibodies (including M2, LKM-1, LC-1, SLA/LP) and Anti Smooth Muscle Antibody were all negative.

Serologies for hepatitis A, B, C, E and Human Immunodeficiency Virus were negative as well. Her renal function was normal.

She has no history of allergies or atopy and stool samples sent for parasites were negative twice. She had no new symptoms, had a good appetite without weight loss and was well and stable with no other organ involvement.

She underwent an ultrasound of the abdomen which showed a prominent pancreatic duct and biliary sludge in the gallbladder. It was normal otherwise with a negative sonographic Murphy's sign. There were no gallstones, no biliary tree dilation and the common bile duct (CBD) measured 5 mm.

She was further investigated with a magnetic resonance cholangiopancreatography (MRCP) which showed stones in the gallbladder with no evidence of cholecystitis. There was also prominence of the CBD at 9mm without a centrally obstructing stone, stricture or definite mass. The pancreatic duct was prominent with borderline dilated calibre but no obstructing lesion was detected. There were also several prominent/borderline dilated subsegmental ducts in segment VIII, V and II, and underlying strictures with mild periportal oedema (Figure 1).

Our patient went on to do an endoscopic ultrasound (EUS) for further evaluation of her CBD and PD prominence and exclude an ampullary lesion. The EUS showed a mildly thickened CBD wall which was unremarkable endosonographically. The biliary tree was not dilated. No intervention was done as there were no significant endosonographic abnormalities.

Our working diagnosis was Eosinophilic Cholangitis

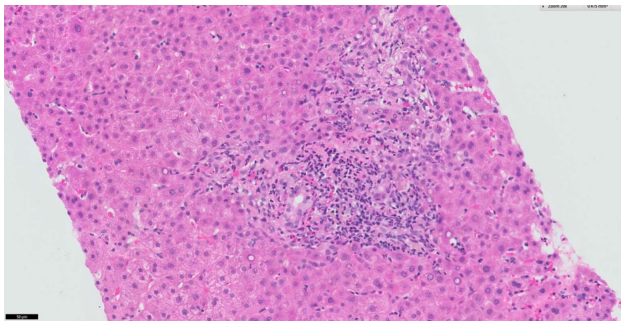

Figure 2 Histology from liver biopsy at 20 × magnification with HE staining: Portal and bile duct inflammation with up to 18 Eos/HPF. There is bile ductular proliferation and portal tract oedema.

in view of the biliary strictures and dilation seen on MRCP with eosinophilia and raised serum IgE.

We have excluded biliary stones and an ampullary tumour. Autoimmune and viral serology were also negative. Drug induced liver injury was unlikely as she had no exposure.

A liver biopsy was performed which confirmed portal and bile duct inflammation with a significant number of eosinophils of up to 18 per HPF (Figure 2). There was mild to moderate portal inflammatory cell infiltrate, predominantly composed of neutrophils and lymphocytes with moderate numbers of eosinophils. There was also bile ductular proliferation and portal tract oedema. No evidence of ductopenia, florid duct lesion, cholestasis, granuloma or neoplasia. Special stains did not show evidence of fibrosis. There was no conspicuous HBsAg, copper-associated protein, PASD positive or significant iron deposits. No increase in IgG4 positive cells were noted on immunohistochemistry.

Our patient was started on oral budesonide 9 mg/d. After one month of oral budesonide, her eosinophilia resolved and her LFT showed marked improvement with almost halved ALP (476 U/L) and ALT (125 U/L) values. Her LFT normalised after 6 mo. The patient declined a repeat liver biopsy but a repeat MRCP was done at 4 mo of treatment and showed overall improvement of the biliary dilation and strictures seen previously. Her oral budesonide was tapered down after 6 mo and subsequently discontinued after 9 mo.

DISCUSSION

Eosinophilic cholangitis (EC) is an uncommon and unknown cause of indeterminate biliary stricture and there is no consensus on a diagnostic criterion available. Matsumoto *et al*[1] proposed the following findings to diagnose EC: (1) Wall thickening or stenosis of the biliary system; (2) histopathological findings of eosinophilic infiltration; and (3) reversibility of biliary abnormalities without treatment or following steroid treatment.

The degree of eosinophilic infiltration has not been established either. In fact, there are case reports of Eosinophilic cholangitis with normal liver biopsies[2]. As a general guideline, Eos/HPF are significant when > 15 in the gastrointestinal tract but this has not been specified in EC[3]. Peripheral eosinophilia and obstructive liver function tests results are helpful laboratory findings to consider the diagnosis of EC. However, peripheral eosinophilia is only present in about two-third of cases[4].

A review of 23 cases of eosinophilic cholangitis showed that eight (34.8%) had complete resolution of symptoms with surgery alone and seven (30.4%) improved with the use of oral corticosteroids. The remaining six cases needed a combination of surgery and oral corticosteroids for resolution[4]. Most treatment experience with steroids for eosinophilic cholangitis was with prednisolone.

Budesonide is a corticosteroid immunosuppressive agent that results in interference with cytokine production and inhibition of T lymphocyte activation. It is a second-generation corticosteroid with an affinity for the glucocorticoid receptor that is approximately 15 times greater than that of prednisolone. When taken orally, it has a 90% first-pass metabolism in the liver, allowing it to reach high intrahepatic concentrations before its elimination, significantly limiting its systemic effects[5]. Budesonide has been compared to prednisolone and found to be more effective with fewer adverse effects than prednisolone for liver specific disease such as autoimmune hepatitis[6]. It is prescribed at a dose of 9 mg once a day and shown to be effective in patients with active Crohn's disease and autoimmune hepatitis[7]. Hence, we chose to use budesonide at a dose of 9 mg once a day for our patient based on known evidence of its efficacy at this dose.

EC is a benign condition and should be managed with a trial of corticosteroids before considering more invasive treatment. A recent retrospective study showed an EC prevalence of 2.2% from a cohort of 135 cases of sclerosing cholangitis and post-hoc diagnosis of EC was ascertained in 30% (3/10) of patients where no cause of indeterminate biliary stricture was identified[8]. Our patient was on oral budesonide treatment for 9 mo with biochemical resolution of her eosinophilia and liver function test. She did not exhibit adverse effects from budesonide therapy on outpatient follow up. This case report is the first, to our knowledge, to treat EC with budesonide.

ARTICLE HIGHLIGHTS

Case characteristics

Deranged liver function test with a cholestatic pattern, eosinophilia, raised IgE, intrahepatic biliary stricture.

Clinical diagnosis

Eosinophilic cholangitis.

Differential diagnosis

Biliary stone, pancreaticobiliary malignancy, drug induced liver injury.

Laboratory diagnosis

Eosinophilic cholangitis.

Imaging diagnosis
Biliary stricture and dilation.

Pathological diagnosis
Eosinophilic cholangitis.

Treatment
Budesonide 9 mg once a day.

Related reports
There are no previous reports of treating eosinophilic cholangitis with Budesonide. But there are reports of successful treatment with prednisolone. Please see reference No. 2.

Experiences and lessons
This is a rare case of eosinophilic cholangitis and the first time in literature, to be successfully treated with budesonide. The patient did not experience any side effects or steroid toxicity. In the future, with further evidence, budesonide might be a reasonable first line treatment for eosinophilic cholangitis as it is safer than prednisolone.

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