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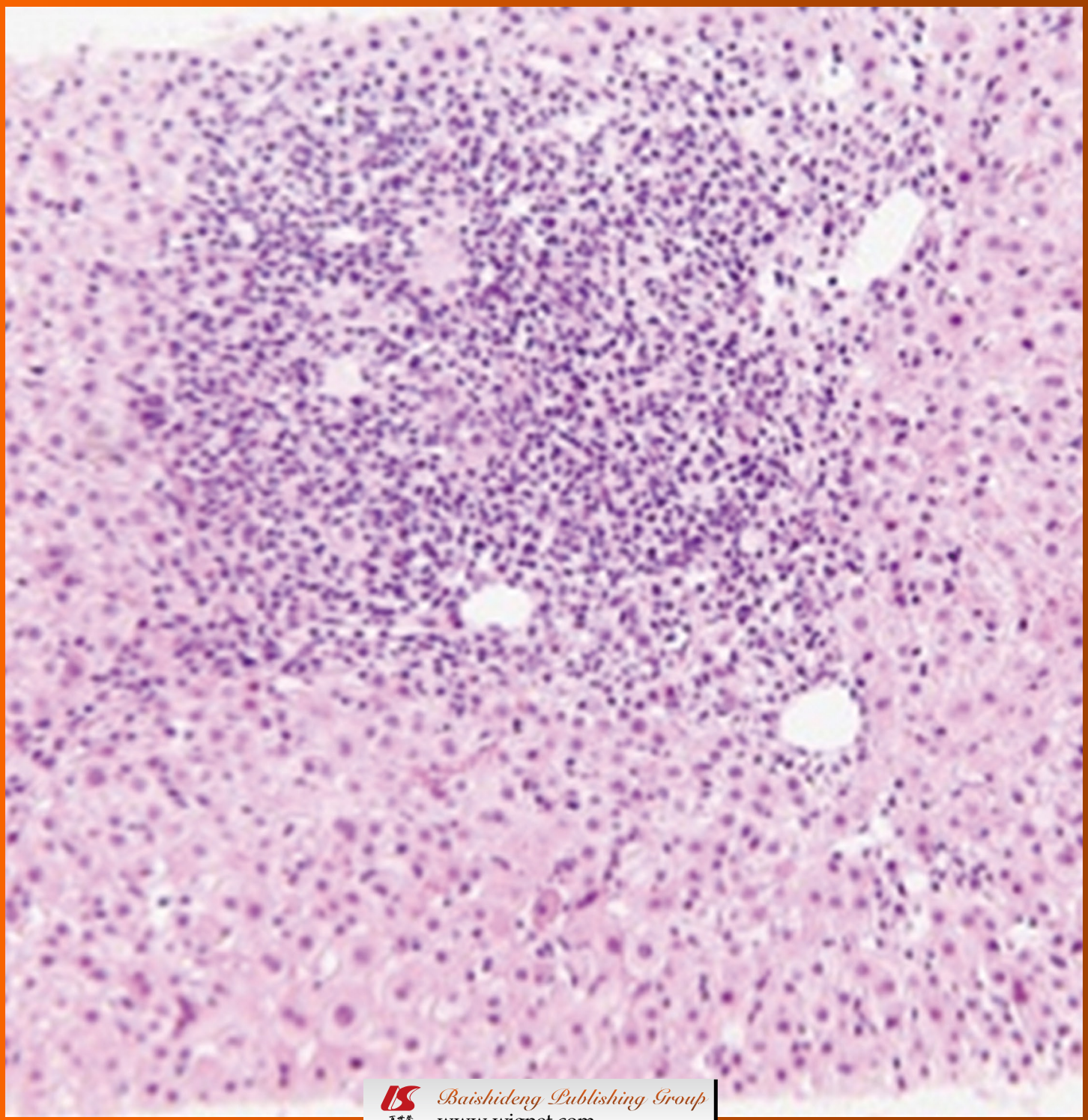

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BRIEF ARTICLE

Natural history of untreatable hepatocellular carcinoma: A retrospective cohort study

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Abstract

AIM: To investigate the clinical course of untreatable hepatocellular carcinoma (HCC) identified at any stage and to identify factors associated with mortality.

METHODS: From January 1999 to December 2010, 320 out of 825 consecutive patients with a diagnosis of HCC and not appropriate for curative or palliative treatments were followed and managed with supportive therapy. Cirrhosis was diagnosed by histological or clinical features and liver function was evaluated according to Child-Pugh score. The diagnosis of HCC was performed by Ultra-Sound guided biopsy or by multiphasic contrast-enhanced computed tomography or gadolinium-enhanced magnetic resonance imaging. Data were collected for each patient including all clinical, laboratory and imaging variables necessary for the outcome prediction staging systems considered. HCC staging was performed according Barcelona Clinic Liver Cancer (BCLC) and Cancer of the Liver Italian Program scores. Follow-up time was defined as the number of months from the diagnosis of HCC to death. Prognostic baseline variables were analyzed by multivariate Cox analysis to identify the independent predictors of survival.

RESULTS: Seventy-five per cent of patients had hepatitis C. Ascites was present in 169 patients (53%), while hepatic encephalopathy was present in 49 patients (15%). The Child-Pugh score was class A in 105 patients (33%), class B in 142 patients (44%), and class C in 73 patients (23%). One hundred patients (31%) had macroscopic vascular invasion and/or extrahepatic spread of the tumor. A single lesion > 10 cm was observed in 34 patients (11%), while multinodular HCC was present in 189 patients (59%). Thirty nine patients (12%) were BCLC early (A) stage, 55 (17%) were BCLC intermediate (B) stage, 124 (39%) were BCLC advanced (C) stage, and 102 (32%) were end-stage BCLC (D). At the time of this analysis (July 2011), 28 (9%) patients were still alive. Six (2%) patients who were lost during follow-up were censored at the last visit. The overall median survival was 6.8 mo, and the 1-year survival was 32%. The 1-year survival according to BCLC classes was 100%, 79%, 12% and 0%, for BCLC A, B, C and D, respectively. There was a significant difference in survival between each BCLC class. The median survival of patients of BCLC stages A, B, C and D was 33, 17.4, 6.9, and 1.8 mo, respectively ($P < 0.05$ for comparison between stages). The median survival of Child-Pugh A, B and C classes were 9.8 mo

(range 6.4-13), 6.1 (range 4.9-7.3), and 3.7 (range 1.5-6), respectively ($P < 0.05$ for comparison between stages). By univariate analysis, the variables significantly associated to an increased liklihood of mortality were Eastern Cooperative Oncology Group performance status (PS), presence of ascites, low level of albumin, elevated level of bilirubin, international normalized ratio (INR) and Log-[(α fetoprotein (AFP)]. At multivariate analysis, mortality was independently predicted by bad PS ($P < 0.0001$), high INR values ($P = 0.0001$) and elevated Log-(AFP) levels ($P = 0.009$).

CONCLUSION: This study confirms the heterogeneous behavior of untreated HCC. BCLC staging remains an important prognostic guide and may be important in decision-making for palliative treatment.

Key words: Hepatocellular carcinoma; Liver; Cancer; Survival; Prognosis; Natural history

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INTRODUCTION

Hepatocellular carcinoma (HCC) is associated with a high rate of mortality[1] and, despite extensive application of intensive surveillance programs, considerable therapeutic progress, and technological improvement observed over the past few years, prognosis of this tumor is poor even when treatments have been considered potentially curative[2].

Curative treatments for early-stage tumors include liver transplantation, resection and percutaneous ablation. Transarterial chemoembolization (TACE) and sorafenib can improve survival for patients with intermediate and advanced tumors, respectively[3].

Although in two large-scale studies[4,5], sorafenib has been shown to improve survival in unresectable HCC patients with well-preserved liver function, response rates remain poor. Moreover, recent studies showed that tolerability was moderate and that most patients need reduction or interruption of treatment[6-8]. So, there is a need for further properly designed randomized controlled trials (RCTs) to assess the survival benefits of second-line systemic therapies. The design of such trials would require an accurate estimation of the survival of patients with untreated disease, preferably with stratification according to known prognostic factor. In addition, as soon as the results of such trials are available, patients and their physicians will become aware of the natural history of the untreated disease will be better able to decide whether or not to accept other palliative treatments.

The natural course of unresectable HCC has recently been evaluated in a meta-analysis[9] which analyzed the survival rates of the placebo and untreated arms of several RCTs on HCC patients, showing that the 1- and 2-year survival is extremely heterogeneous.

For ethical reasons it is not possible to evaluate the natural history of early HCC in RCTs. However a milestone paper[10] published in 1989 showed that 1- and 2-year overall survival (OS) of asymptomatic patients with HCC and cirrhosis was 96% and 50%, respectively.

To provide updated survival data on untreated HCC in Italy, we analyzed the clinical data of a cohort of HCC patients followed in our Liver Unit.

MATERIALS AND METHODS

Patients

From January 1999 to December 2010, 825 consecutive patients with cirrhosis and a new diagnosis of HCC were observed at our Liver Unit. Cirrhosis was diagnosed by histological or clinical features and the liver function was evaluated according to Child-Pugh score. The diagnosis of HCC was performed by ultrasound guided biopsy or by multiphasic contrast-enhanced computed tomography or gadolinium-enhanced magnetic resonance imaging. Performance status (PS) was scored according to the Eastern Cooperative Oncology Group (ECOG)[11].

All patients were evaluated according to European Association for the Study of the Liver criteria[12] up to 2005, and to American Association for the Study of Liver Diseases criteria[13] from January 2006. HCC staging and the choice of treatment were performed according to the Barcelona Clinic Liver Cancer (BCLC) schedule[14].

Patients with early tumors (BCLC A) were considered for curative therapies [resection, orthotopic liver transplantation (OLT), or radiofrequency thermal ablation (RFTA)]. TACE was performed in patients at intermediate stage (BCLC B) according to BCLC and in early-stage (BCLC A) patients for whom percutaneous RFTA was not feasible because of tumor location (proximity to gallbladder, biliary tree, or blood vessel) or in whom surgery could not be performed because of comorbidities[6,15-19]. Combined treatments were used when indicated to achieve a better radical cure[20]. Starting July 2008, patients with advanced HCC and patients with an intermediate HCC who were not eligible for or failed loco-ablative therapies were treated with sorafenib.

The current study analyzed the natural course of patients with HCC at any stage who were untreated for any cause. Follow-up was censored on July 31, 2011. The main causes for non-treatment were the presence of severe co-morbidities or impaired PS[3,4], advanced age,

refusal of treatment, diffuse or massive tumor with or without macro-vascular invasion or extra-hepatic spread before the advent of sorafenib, poor residual liver function (Child-Pugh > B8) precluding OLT.

Outcome

The primary outcome measure in this analysis was survival. Follow-up time was defined as the number of months from the diagnosis of HCC to death. All subjects were followed as outpatients or inpatients at our Liver Unit and clinical data were collected by telephone follow-up when clinical worsening did not allow the patient to present for medical controls.

Statistical analysis

Data collected for each patient included all clinical, laboratory and imaging variables necessary for the outcome prediction staging systems considered. Patients were also stratified according to Child-Pugh, BCLC and Italian (Cancer of the Liver Italian Program) classifications. Continuous variables were expressed as mean ± SD. The Kaplan-Meier estimator was applied to survival. Differences in the survival rate were assessed by log-rank testing. Variables listed in Table 1 were analyzed using univariate analysis. All variables with a *P*-value less than 0.05 by univariate analysis were subjected to multivariate analysis. The multivariate analysis was performed by the Cox proportional hazard model. All statistical analyses were performed with the Statistical Analysis System (SAS) version 8.1 (SAS Institute, Inc., Cary, NC, United States).

RESULTS

Patient features at baseline

The study population consisted of 320 patients with HCC secondary to cirrhosis of various etiologies. The demographical, clinical and tumor staging features of the 320 patients are given in Table 1. Chronic hepatitis C virus infection was the dominant etiology (75%).

At presentation, the Child-Pugh score was class A in 105 patients (33%), class B in 142 patients (44%), and class C in 73 patients (23%). Ascites was present in 169 patients (53%), while hepatic encephalopathy was present in 49 patients (15%).

Regarding the features of HCC, 100 patients (31%) had macroscopic vascular invasion and/or extra-hepatic spread of the tumour. A single lesion > 10 cm was observed in 34 patients (11%), while multinodular HCC was present in patients 189 (59%). Thirty nine patients (12%) were BCLC early (A) stage, 55 (17%) were BCLC intermediate (B) stage, 124 (39%) were BCLC advanced (C) stage, and 102 (32%) were end-stage BCLC (D).

At the time of this analysis (July 2011), 28 (9%) patients were still alive. Six (2%) patients who were lost during follow-up were censored at their last visit.

Table 1 Baseline demographic, laboratory, clinical and tumour staging characteristics of 320 untreated hepatocellular carcinoma patients (mean ± SD) *n* (%)

Variable	Patients (*n* = 320)
Age (yr)	68 ± 9.8
Sex	
Male	226 (71)
Female	94 (29)
Etiology of cirrhosis	
Hepatitis C only	241 (75)
Hepatitis B only	27 (8)
Alcohol abuse only	12 (4)
Multiple	9 (3)
Other	31 (10)
Biopsy-proven HCC diagnosis	60 (19)
Non-invasive HCC diagnosis	260 (81)
ECOG performance status[1]	
0	94 (30)
1-2	123 (38)
3-4	103 (32)
Hepatic encephalopathy	
None	271 (85)
Grades Ⅰ-Ⅱ	39 (12)
Grades Ⅲ-Ⅳ	10 (3)
Ascites	
Absent	151 (48)
Slight	122 (38)
Moderate-severe	47 (14)
Child-pugh score	8 ± 2
Child-pugh classes	
A	105 (33)
B	142 (44)
C	73 (23)
Albumin (g/dL)	3.1 ± 0.6
International normalized ratio	1.4 ± 0.4
Total bilirubin (mg/dL)	2.8 ± 4.2
Platelet × 10^3/mmc	112 ± 80
Uninodular HCC	131 (41)
Multinodular HCC	189 (59)
Single lesion > 10 cm	34 (11)
Macroscopic vascular invasion and/or extrahepatic spread	100 (31)
AFP (ng/mL)	
Median	35
Range	1-115.000
AFP ⩾ 200 ng/dL	79 (24)
BCLC stage	
A (early)	39 (12)
B (intermediate)	55 (17)
C (advanced)	124 (39)
D (end-stage)	102 (32)
CLIP score	
0	23 (7)
1	49 (15)
2	127 (40)
3	67 (21)
4	34 (11)
5	17(5)
6	3 (1)

[1]Eastern Cooperative Oncology Group-Performance Status. AFP: α fetoprotein; BCLC: Barcelona Clinic Liver Cancer; CLIP: Cancer of LiverItalian Program; HCC: Hepatocellular carcinoma; ECOG: Eastern Cooperative Oncology Group.

Survival

The median OS was 6.8 mo (95%CI: 5.8-7.7), corresponding to 33% of the patients being alive at 1 year. The 1-year survival according to BCLC class was 100%,

Table 2 Summary of follow-up in 320 untreated hepatocellular carcinoma patients (%)

Outcome	Patients (n = 320)
Death	292 (91)
Overall survival	
Median (95%CI) (mo)	6.8 (5.8-7.7)
1-yr survival rate	32
2-yr survival rate	13
BCLC A (early stage) survival	
Median (95%CI) (mo)	33 (20-46)
1-yr survival rate	100
2-yr survival rate	57
3-yr survival rate	41
BCLC B (intermediate stage) survival	
Median (95%CI) (mo)	17.4 (14.8-20)
1-yr survival rate	79
2-yr survival rate	22
3-yr survival rate	5
BCLC C (advanced stage) survival	
Median (95%CI) (mo)	6.9 (6.3-7.3)
1-yr survival rate	12
BCLC D (end-stage) survival	
Median (95%CI) (mo)	1.8 (1.2-2.4)
1-yr survival rate	0

BCLC: Barcelona Clinic Liver Cancer classification.

79%, 12% and 0%, for BCLC A, B, C and D, respectively (Table 2 and Figure 1).

There was a significant progressive difference in survival between each BCLC class. The median survival of BCLC A (33 mo; range 20-46) was significantly longer than that of BCLC B (17.4 mo; range 14.8-20), BCLC C (6.9 mo; range 6.3-7.3), and BCLC D (1.8 mo; range 1.2-2.4).

The median survival of Child-Pugh A, B and C classes were 9.8 mo (range 6.4-13), 6.1 mo (range 4.9-7.3), and 3.7 mo (range 1.5-6), respectively ($P < 0.05$ for comparison between stages).

By univariate analysis, the variables significantly associated to an increased likelihood of mortality were ECOG PS, presence of ascites, low level of albumin, elevated level of bilirubin, international normalized ratio (INR) and Log-[α fetoprotein (AFP)]. Cox regression analysis showed that PS [hazard ratio (HR) 2.875, 95%CI: 2.547-3.245, $P < 0.0001$], INR (HR 1.811, 95%CI: 1.328-2469, $P = 0.0001$), and Log-(AFP) (HR 1.078, 95%CI: 1.018-1.142, $P = 0.009$) were independent risk factors for mortality (Table 3).

DISCUSSION

HCC secondary to cirrhosis is a complex and heterogeneous disease with wide variations during its clinical course. In this context, the management of cirrhotic patients with neoplasm is a major clinical issue[21,22].

A better knowledge of the natural history of the tumor as well as the development of clinically based staging systems, such the BCLC classification which stratifies patients according to the stage of the tumor and liver disease, has meant that life expectancies can be confidently predicted, and the appropriate treatment can be chosen according to stage.

Table 3 Multivariate Cox-regression models for predicting over all survival in 320 patients with hepatocellular carcinoma patients in cirrhosis

Variable	HR	95%CI	P value
Performance status[1]	2.875	2.547-3.245	< 0.0001
INR	1.811	1.328-2469	0.0001
Log-(AFP)	1.078	1.018–1.142	0.009
Albumin	-	-	-
Total Bilirubin	-	-	-
Presence of ascites	-	-	-

[1]Eastern Cooperative Oncology Group-Performance Status. HR: Hazard ratio; INR: International Normalized Ratio; AFP: α fetoprotein.

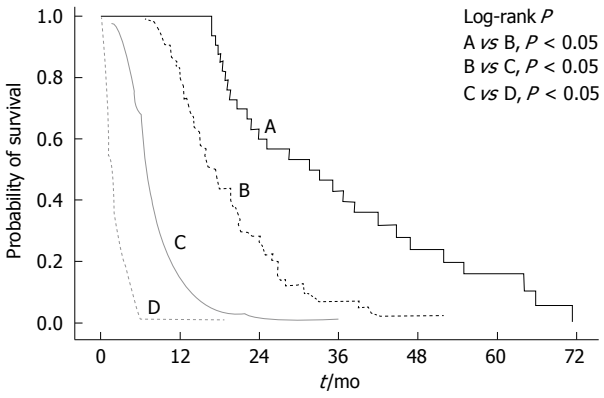

Figure 1 Kaplan-Meier analysis of 320 untreated hepatocellular carcinoma patients. Survival according to Barcelona Clinic Liver Cancer classification.

This study shows that in patients with untreated HCC, survival can be predicted from information collected by the physician as part of the initial assessment. In fact, the identified prognostic factors (PS, INR and AFP) are easily measured. Decreased PS has been previously found to have prognostic value in patients with HCC[9,14]. In our cohort, advanced liver diseases, assessed by high INR was associated with improvement in survival, while elevated serum AFP reflects the degree of cellular differentiation and thus the spread of the tumor. Moreover, our study confirms that the BCLC staging classification sensitively identifies HCC patients with a good or unfavorable prognosis.

Although, the median survival for early stage observed in our study was good (33 mo), data on survival rates of early HCC patients confirm, even in absence of data from RCT, the effectiveness of any current treatment for this cancer.

Clearly, the impact of sorafenib for patients with advanced HCC and with intermediate HCC who were unfit or failed to respond to ablative therapies, is a landmark in the treatment of liver cancer. However, given the high rate of therapy discontinuation for adverse events or radiological progression, data on survival of untreated intermediate/advanced stage patients could give useful information in the design of RCTs on second-line treatment with new agents after failure of sorafenib therapy[23,24].

In our cohort, HCC patients in BCLC D stage at baseline have a 1-year survival of less than 5%. Given this poor life expectancy, BCLC suggests only symptomatic treatment.

The study had some bias. Firstly, it was conducted retrospectivelyalthough, because the only defined endpoint was survival, it is unlikely that the results were affected. Another weakness is the lack of data on molecular factors, such as gene expression profiling, which can have some impact on patient outcome[25,26].

The treatment of HCC has changed dramatically. Years ago, there were no safe or reliable therapies for patients diagnosed with this cancer and their prognosis was uniformly grim. Now, all stages of the disease may receive effective therapy and current research will expand the existing benefits. However, the current therapeutic approach still needs significant improvement. Firthermore, the therapeutic options for patients with advanced HCC have limited impact and thus, development of new agents and strategies for this group of patients is of majorimportance.

In untreated HCC patients, the available evidence is sufficient to conclude that poor PS, high INR values and high AFP levels are associated with worse prognosis. BCLC staging classification sensitively identifies HCC untreated patients with a good or unfavorable prognosis. Patients at BCLC end-stage should only receive symptomatic treatment.

COMMENTS

Background

Hepatocellular carcinoma (HCC) is an insidious disease, with no particular or specific signs and symptoms of manifestation and whose behavior is usually unpredictable. Its natural history is also dependent on functional impairment of the underlying liver disease which often limits the application of therapeutic modalities and influences survival.

Research frontiers

The spontaneous course of the unresectable disease has recently been evaluated in a meta-analysis which analyzed the survival rates of the placebo and untreated arms of several randomized controlled trials (RCTs) on HCC patients, showing that the 1- and 2-year survival is extremely heterogeneous.

Innovations and breakthroughs

For ethical reasons it is not possible to evaluate the natural history of early HCC in RCTs. In patients with untreated HCC, survival can be predicted from information collected by the physician as a part of the initial assessment. In fact, the prognostic factors identified [performance status (PS), international normalized ratio (INR) and α-fetoprotein (AFP)] are easily measured. Moreover, the Barcelona Clinic Liver Cancer (BCLC) staging classification sensitively identifies HCC untreated patients with a good or unfavorable prognosis, and patients at BCLC end-stage should only receive symptomatic treatment.

Applications

Knowing the spontaneous outcome of HCC is important for designing RCTs of new therapeutic approaches, for assessing the validity of biological and radiological surrogate markers, and in controlling for confounding factors in observational studies.

Peer review

The study entitled "Natural history of untreatable HCC: A retrospective cohort study" by Giuseppe Cabibbo *et al* describes the natural history of untreated patients with HCC. Poor prognosis (survival) is related to bad PS, high INR and AFP values. The study is interesting for the readers even though it does not include any molecular analysis which could give additional information.

REFERENCES

1 **Llovet JM**, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, Sherman M, Schwartz M, Lotze M, Talwalkar J, Gores GJ. Design and endpoints of clinical trials in hepatocellular carcinoma. *J Natl Cancer Inst* 2008; **100**: 698-711

2 **Bruix J**, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; **53**: 1020-1022

3 **El-Serag HB**. Hepatocellular carcinoma. *N Engl J Med* 2011; **365**: 1118-1127

4 **Llovet JM**, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378-390

5 **Cheng AL**, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Burock K, Zou J, Voliotis D, Guan Z. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10**: 25-34

6 **Iavarone M**, Cabibbo G, Piscaglia F, Zavaglia C, Grieco A, Villa E, Cammà C, Colombo M. Field-practice study of sorafenib therapy for hepatocellular carcinoma: a prospective multicenter study in Italy. *Hepatology* 2011; **54**: 2055-2063

7 **Pinter M**, Sieghart W, Hucke F, Graziadei I, Vogel W, Maieron A, Königsberg R, Weissmann A, Kornek G, Matejka J, Stauber R, Buder R, Grünberger B, Schöniger-Hekele M, Müller C, Peck-Radosavljevic M. Prognostic factors in patients with advanced hepatocellular carcinoma treated with sorafenib. *Aliment Pharmacol Ther* 2011; **34**: 949-959

8 **Schütte K**, Zimmermann L, Bornschein J, Csepregi A, Rühl R, Ricke J, Malfertheiner P. Sorafenib therapy in patients with advanced hepatocellular carcinoma in advanced liver cirrhosis. *Digestion* 2011; **83**: 275-282

9 **Cabibbo G**, Enea M, Attanasio M, Bruix J, Craxì A, Cammà C. A meta-analysis of survival rates of untreated patients in randomized clinical trials of hepatocellular carcinoma. *Hepatology* 2010; **51**: 1274-1283

10 **Cottone M**, Virdone R, Fusco G, Orlando A, Turri M, Caltagirone M, Maringhini A, Sciarrino E, Demma I, Nicoli N. Asymptomatic hepatocellular carcinoma in Child's A cirrhosis. A comparison of natural history and surgical treatment. *Gastroenterology* 1989; **96**: 1566-1571

11 **Oken MM**, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5**: 649-655

12 **Bruix J**, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, Pagliaro L, Colombo M, Rodés J. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001; **35**: 421-430

13 **Bruix J**, Sherman M. Management of hepatocellular carcinoma. *Hepatology* 2005; **42**: 1208-1236

14 **Llovet JM**, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis* 1999; **19**: 329-33

15 **Cabibbo G**, Genco C, Di Marco V, Barbara M, Enea M, Parisi P, Brancatelli G, Romano P, Craxì A, Cammà C. Predicting survival in patients with hepatocellular carcinoma treated by transarterial chemoembolisation. *Aliment Pharmacol Ther* 2011; **34**: 196-204

16 **Sandonato L**, Cipolla C, Fulfaro F, Lo Re G, Latteri F, Terranova A, Mastrosimone A, Bova V, Cabibbo G, Latteri MA. Minor hepatic resection using heat coagulative necrosis. *Am*

Surg 2009; **75**: 1213-1219
17 **Cammà C**, Di Marco V, Cabibbo G, Latteri F, Sandonato L, Parisi P, Enea M, Attanasio M, Galia M, Alessi N, Licata A, Latteri MA, Craxì A. Survival of patients with hepatocellular carcinoma in cirrhosis: a comparison of BCLC, CLIP and GRETCH staging systems. *Aliment Pharmacol Ther* 2008; **28**: 62-75
18 **Latteri F**, Sandonato L, Di Marco V, Parisi P, Cabibbo G, Lombardo G, Galia M, Midiri M, Latteri MA, Craxì A. Seeding after radiofrequency ablation of hepatocellular carcinoma in patients with cirrhosis: a prospective study. *Dig Liver Dis* 2008; **40**: 684-689
19 **Cammà C**, Di Marco V, Orlando A, Sandonato L, Casaril A, Parisi P, Alizzi S, Sciarrino E, Virdone R, Pardo S, Di Bona D, Licata A, Latteri F, Cabibbo G, Montalto G, Latteri MA, Nicoli N, Craxì A. Treatment of hepatocellular carcinoma in compensated cirrhosis with radio-frequency thermal ablation (RFTA): a prospective study. *J Hepatol* 2005; **42**: 535-540
20 **Cabibbo G**, Latteri F, Antonucci M, Craxì A. Multimodal approaches to the treatment of hepatocellular carcinoma. *Nat Clin Pract Gastroenterol Hepatol* 2009; **6**: 159-169
21 **Cabibbo G**, Palmeri L, Palmeri S, Craxì A. Should cirrhosis change our attitude towards treating non-hepatic cancer? *Liver Int* 2012; **32**: 21-27
22 **Cabibbo G**, Rolle E, De Giorgio M, Genco C, Pressiani T, Spada F, Sacco R. Management of cirrhotic patients with hepatocellular carcinoma treated with sorafenib. *Expert Rev Anticancer Ther* 2011; **11**: 1807-1816
23 **Villanueva A**, Llovet JM. Second-line therapies in hepatocellular carcinoma: emergence of resistance tzfo sorafenib. *Clin Cancer Res* 2012; **18**: 1824-1826
24 **Villanueva A**, Llovet JM. Targeted therapies for hepatocellular carcinoma. *Gastroenterology* 2011; **140**: 1410-1426
25 **Villanueva A**, Newell P, Chiang DY, Friedman SL, Llovet JM. Genomics and signaling pathways in hepatocellular carcinoma. *Semin Liver Dis* 2007; **27**: 55-76
26 **Villanueva A**, Hoshida Y, Toffanin S, Lachenmayer A, Alsinet C, Savic R, Cornella H, Llovet JM. New strategies in hepatocellular carcinoma: genomic prognostic markers. *Clin Cancer Res* 2010; **16**: 4688-4694

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BRIEF ARTICLE

Centrilobular necrosis in acute presentation of Japanese patients with type 1 autoimmune hepatitis

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Abstract

AIM: To compare clinicopathological features of acute presentation of type 1 autoimmune hepatitis (AIH) with or without centrilobular necrosis (CN).

METHODS: Our study comprised 41 patients with biopsy-proven acute presentation (acute exacerbation phase 36, acute hepatitis phase 5) of type 1 AIH at our hospital from 1975 to 2009. Elevated serum alanine aminotransferase (ALT) (> 5x upper limit of normal) identified acute presentation of the disease. We compared clinicopathological features of these AIH patients with or without CN. The data used for analysis included patient background (age, sex, type of disease, presence of complications with other autoimmune diseases, human leukocyte antigen, and International Autoimmune Hepatitis Group score), clinical parameters at presentation (ALT, alkaline phosphatase, IgG, anti-nuclear antibodies, and anti-smooth muscle antibodies), histology and therapy.

RESULTS: CN was found in 13 (31.7%) patients with acute presentation (acute exacerbation phase 10, acute hepatitis phase 3) of AIH. Serum IgG levels of patients with CN were significantly lower than those of patients without CN (mean: 2307 mg/dL *vs* 3126 mg/dL, $P < 0.05$), while antinuclear antibody-negative rates were significantly higher (30.7% *vs* 3.5%, $P < 0.05$). However, other clinical features were similar between the two groups. The frequency of advanced fibrosis in patients with CN was significantly lower than in patients without CN (F0-2: 84.6% *vs* 35.7%, F3-4: 15.4% *vs* 64.3%, $P < 0.05$). Other histological features were similar between the two groups. Although there was no significant difference between groups when evaluated using the revised original score (12 *vs* 14), the simplified AIH score of patients with CN was significantly lower (6 *vs* 7, $P < 0.05$). Frequency of DR4 was similar between patients with and without CN.

CONCLUSION: CN is observed in both Japanese patients with acute hepatitis phase and acute exacerbation phase of type 1 AIH, although AIH with CN often shows clinical features of the genuine acute form.

Key words: Autoimmune hepatitis; Centrilobular necrosis; Acute presentation; Acute exacerbation phase; Acute hepatitis phase

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INTRODUCTION

Autoimmune hepatitis (AIH) manifests as chronic liver inflammation of unknown cause. AIH generally affects young to middle-aged women, and is associated with the presence of autoantibodies and hypergammaglobulinemia[1]. The histological hallmark of AIH is interface hepatitis, although other histological findings are compatible with the disease. Human leukocyte antigen DR status is considered to affect the clinical features of patients with type 1 AIH. In Japanese patients, DR4 is dominantly associated with the disease. Patients with DR4 are typically older and respond better to corticosteroid treatment than those with DR3[2]. Centrilobular necrosis (CN) is a non-specific histological finding caused by hepatotoxins, such as acetaminophen, paracetamol, thioacetamide, tetrachloride, congestive hepatic injury and cardiac hepatopathy due to acute right side cardiac failure[3-5]. CN probably reflects early stage AIH detected primarily in patients with an acute onset[6-8]. Cases of acute presentation of AIH have frequently been reported. The first report showed two AIH cases presenting histologically acute hepatitis[9]. Other reports revealed cases of the clinically acute phase of AIH not associated with typical AIH[7,10]. Pathological examination of acute presentations revealed that the cases with CN demonstrate different characteristics from those of typical AIH[11]. Moreover, a recent report indicated that it is possible to distinguish the acute phase of AIH from the acute exacerbation phase of AIH by checking the existence of both CN and portal inflammation[12]. Recently, it has been reported from the AIH study group in Japan[13] that there are two types of acute presentation in patients with AIH, acute exacerbation phase and acute hepatitis phase. Here, we compared the clinicopathological features of acute presentation of AIH with and without CN.

MATERIALS AND METHODS

Patients

Our study comprised 41 patients with biopsy-proven acute presentation of AIH at our hospital from 1975 to 2009 (38 women and 3 men, mean age: 52.2 years). These patients were reviewed according to the revised original scoring system or the simplified scoring system of the International Autoimmune Hepatitis Group (IAIHG)[14-16]. We only applied pre-treatment criteria for AIH diagnosis. In the revised original system, scores of 10 to 15 points support a probable diagnosis while scores greater than 15 points support a definitive diagnosis. With the simplified system, a score of 6 points constitutes a probable diagnosis as a definitive diagnosis requires a score of 7 or more points. None of the patients showed evidence of other liver diseases such as viral hepatitis, haemochromatosis, Wilson's disease, primary biliary cirrhosis or non-alcoholic steatohepatitis. We excluded patients with overlapping syndromes and patients with a daily alcohol intake of > 50 g (men) or > 25 g (women).

The data used for analysis included patient background (age, sex, type of disease, presence of complications with other autoimmune diseases, HLA, and IAIHG score), clinical parameters at presentation [alanine aminotransferase (ALT), alkaline phosphatase, IgG, anti-nuclear antibodies (ANA), and anti-smooth muscle antibodies (ASMA)], histology and therapy.

Serology and histology

ANA and ASMA were detected by indirect immunofluorescence using human epithelial (HEp-2) cells or frozen rat kidney sections. Elevated serum ALT (> 5x upper limit of normal) identified acute presentation of the disease. Patients with acute presentation of the disease with histological evidence of chronic hepatitis, such as the presence of fibrosis and inflammatory cell infiltrations in the portal tracts with interface hepatitis, were diagnosed acute exacerbation phase. Patients with acute presentation of disease but no history of any prior liver disease and no histological evidence of chronic hepatitis were diagnosed acute hepatitis phase. Using the simplified criteria, three characteristics are used for liver histology grading. Interface hepatitis, lymphocytic/lymphoplasmacytic infiltrates in portal tracts and extending into lobules, and emperipolesis and hepatic rosette formation are regarded as typical for AIH diagnosis. Therefore, the presence of all three features is required to be considered "typical" AIH liver histology. However, chronic hepatitis with lymphocytic infiltration but without all the features considered to be typical is compatible with AIH liver histology. Liver histology was considered "atypical" for AIH when showing signs of other diagnosis. Liver biopsy specimens diagnosed as chronic hepatitis underwent histological staging based on the classification of Desmet *et al*[17] as follows: No fibrosis (F0), fibrosis confined to portal tracts (F1), periportal or portal-portal septa but intact vascular relationships (F2), fibrosis with distorted structure but no obvious cirrhosis (F3) and probable or definite cirrhosis (F4). Confluent necrosis with inflammation in zone 3 was considered to be CN. Two pathologists blinded to the clinical data assessed histopathological findings. The clinicopathological features of AIH with CN were compared to AIH without CN.

Statistical analysis

We used the student's *t*-test for comparing means, the Mann-Whitney *U*-test for non-normally distributed data and the χ^2 test for differences in distributions between groups. A commercially available computer program (Prism version 4.0a; GraphPad Software, Inc.) was used for all statistical calculations and $P < 0.05$ (two tailed) was considered statistically significant.

Table 1 Clinicopathological data of patients with autoimmune hepatitiswith and without centrilobular necrosis *n* (%)

Abbreviations (normal values)	With CN (*n* = 13)	Without CN (*n* = 28)	*P* value
Mean age (range) (yr)	51.1 (23-80)	52.7 (21-77)	NS
Sex (M/F)	2/11	1/27	NS
ALT (IU/L)	907 (228-3250)	667 (224-1761)	NS
ALP (IU/L)	498 (223-999)	450 (76-883)	NS
IgG (mg/dL)	2307 (1150-3913)	3126 (1294-5449)	< 0.05
ANA neg.	4 (30.7)	1 (3.5)	< 0.05
Other autoimmune disease	4 (30.7)	7 (25.0)	NS
Steroid therapy	11 (84.6)	24 (85.7)	NS
Azathioprine therapy	2 (15.4)	7 (25.0)	NS
AIH score original	12 (6-20)	14 (6-18)	NS
(Median) simplified	6 (3-8)	7 (5-8)	< 0.05
Interface hepatitis	10 (76.9)	26 (92.8)	NS
Portal inflammation	13 (100)	24 (85.7)	NS
Plasma cell infiltration	7 (53.8)	7 (25.0)	NS
Rosette formation	3 (23.1)	3 (12.0)	NS
Fibrosis			
Stage F0-2	11 (84.6)	10 (35.7)	< 0.05
Stage F3-4	2 (15.4)	18 (64.3)	

ALT: Alanineaminotransferase (8-42 IU/L); ALP: Alkaline phosphatase (115-359 IU/L); IgG: Immunoglobulin G (870-1700 mg/dL); ANA: Antinuclear antibody (< 40 ×); NS: Not significant; AIH: Autoimmune hepatitis; CN: Centrilobular necrosis. *P* values were calculated using the Mann-Whitney *U* test and the χ^2 test.

Table 2 Clinical and serological features of 13 autoimmune hepatitis patients with centrilobular necrosis

Case	Age (yr)/ sex	ALT (IU/L)	ALP (IU/L)	IgG (mg/dL)	ANA (titer)	ASMA (titer)	AIH score		HLA	Histology				
							(O)	(S)	DR4	(I)	(L)	(R)	(E)	(F)
1	56/F	831	357	3330	5120	40	20	8	DR4	+	+	+	+	3
2	68/F	1230	479	3215	640	Neg	11	7	-	+	+	+	-	3
3	45/F	3250	423	1800	160	Neg	14	6	DR4	+	+	-	-	2
4	49/M	713	528	2300	640	40	15	7	DR4	+	+	+	-	1
5	23/F	789	596	3913	160	640	17	7	DR4	+	+	-	-	1
6	42/M	1499	972	1150	Neg	Neg	9	3	DR4	-	+	-	-	1
7	57/F	471	223	2266	Neg	20	6	3	DR4	+	+	-	-	1
8	80/F	499	410	1410	40	Neg	11	4	-	+	+	-	-	1
9	52/F	416	458	1280	Neg	160	11	5	-	-	+	-	-	1
10	44/F	1067	377	1370	Neg	Neg	6	3	DR4	-	+	+	-	1
11	44/F	418	273	3503	2560	Neg	14	7	-	+	+	-	-	2
12	35/F	383	335	3086	160	80	17	7	ND	+	+	-	-	1
13	69/F	228	999	1286	160	Neg	13	5	-	+	+	-	-	2

Abbreviations (normal values): ALT: Alanine aminotransferase (8-42 IU/L); ALP: Alkaline phosphatase (115-359 IU/L); IgG: Immunoglobulin G (870-1700 mg/dL); ANA: Antinuclear antibody (< 40 ×); ASMA: Anti-smooth muscle antibody (negative); O: Original system; S: Simplified system; I: Interface hepatitis; L: Lymphocytic/lymphoplasmocytic infiltrates in portal tracts; R: Rosette formation; E: Emperipolesis; F: Fibrosis; Neg: Negative; ND: Not detected; F: Female; M: Male; AIH: Autoimmune hepatitis.

RESULTS

In this study, thirty-six of 41 patients showed acute exacerbation phase and 5 of 41 showed acute hepatitis phase. CN was present in liver biopsies of 13 (31.7%) patients with acute presentation of AIH. Table 1 shows the clinicopathological features of AIH with CN compared to AIH without CN. Three of 13 patients showed acute hepatitis phase and the others were diagnosed as acute exacerbation phase from histological findings. Patients with CN had significantly lower serum IgG levels than patients without CN (mean: 2307 mg/dL *vs* 3126 mg/dL, $P < 0.05$). Patients with CN had significantly higher ANA-negative rates than patients without CN (30.7% *vs* 3.5%, $P < 0.05$ for all measures). However, other clinical features were similar between the two groups (mean age: 51.1 years *vs* 52.7 years, serum alkaline phosphatase: 498 IU/L *vs* 450 IU/L, steroid use: 84.6% *vs* 85.7%, azathioprine use: 15.4% *vs* 25.0%, other autoimmune diseases: 30.7% *vs* 25.0%).

The frequency of advanced fibrosis in patients with CN was significantly lower than in patients without CN (F0-2: 84.6% *vs* 35.7%, F3-4: 15.4% *vs* 64.3%, $P < 0.05$). Other histological features were similar between the two groups (interface hepatitis: 76.9% *vs* 92.8%, portal inflammation: 100% *vs* 85.7%, plasma cell infiltration: 53.8% *vs* 25.0%, hepatocyte rosette formation: 23.1% *vs* 12.0%). Although there was no significant difference between groups when evaluated using the revised original score (12

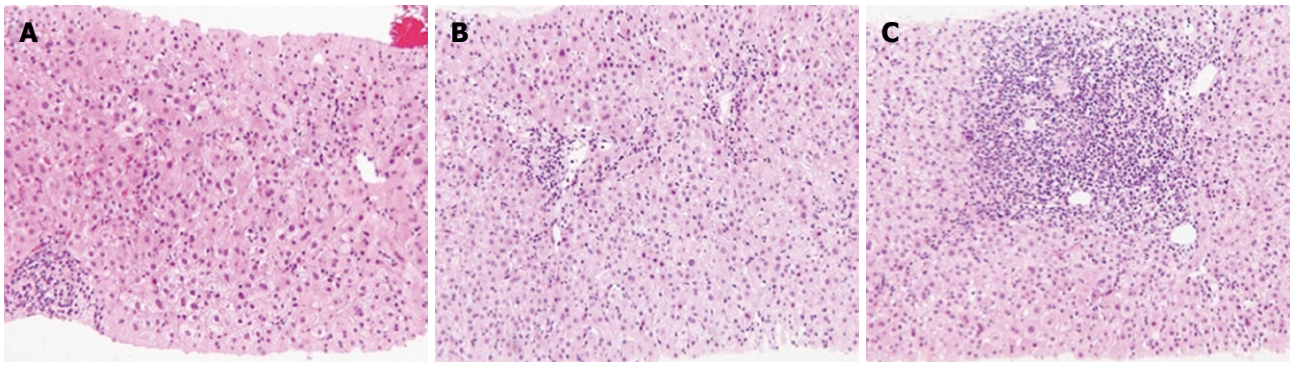

Figure 1 Pathological findings of liver biopsy. A: Liver biopsy from a case of centrilobular necrosis without classic histological features of autoimmune hepatitis that progressed to classic autoimmune hepatitis [hematoxylin staining (HE), 200 ×]; B, C: Centrilobular necrosis with interface hepatitis in liver biopsy (HE, 200 ×).

vs 14), the simplified AIH score of patients with CN was significantly lower (6 *vs* 7, $P < 0.05$).

Table 2 shows the clinical and serological features of the 13 AIH patients with CN. Three patients with CN (cases 6, 7 and 10) had non-diagnostic scores in both the original and simplified systems. Two patients (cases 6 and 10) had undetectable autoantibodies and normal serum IgG levels at initial presentation, and ANA became detectable at second determination, while the other patient (case 7) was positive for hepatitis C virus antibody and negative for hepatitis C virus-RNA. Corticosteroid therapy was effective in these patients. Of 12 patients with CN screened for class II human leukocyte antigen by PCR-rSSO Typing Tests (SRL, Tokyo, Japan), 7 patients (64%) had DR4, and 4 (33%) had DR9. One patient had both DR1 and DR15 while none had DR3. Frequency of DR4 was similar between patients with and without CN.

Three of the 13 CN cases showed acute hepatitis without interface hepatitis (case 6, 9 and 10), but two patients (cases 6 and 10) progressed to classic AIH. Although the liver histology of case 6 with acute hepatitis of unknown cause showed CN without portal inflammation (Figure 1A), a liver biopsy specimen from the same patient 2 mo later revealed interface hepatitis with CN (Figure 1B and C). Patients with CN responded better to corticosteroid treatment than those without.

DISCUSSION

AIH is a form of hepatitis associated with autoantibodies and hypergammaglobulinemia, histologically characterized by chronic active hepatitis showing portal inflammation with fibrosis, interface hepatitis, hepatocyte rosette formation and prominent plasma cell infiltration[18,19]. Cases satisfying the definition of AIH but not fitting the classical disease presentation usually have acute severe presentation, few or no symptoms, atypical histological findings, absent or variant serological markers, concurrent cholangiographic changes, or are male and non-Caucasian[20]. Rare cases of AIH with CN as the dominant finding have been reported. In 1997, Pratt *et al*[11] reported four cases of steroid-responsive hepatitis, presumably AIH with CN. Patients with CN have a higher frequency of acute disease onset and lower frequency of cirrhosis than those without CN[7]. Some of these patients have recurrent CN or progress to classic AIH, although others do not[7,8,11,21]. If CN with autoimmune features represents an early stage of classic AIH, one would expect to encounter it more frequently in patients with acute onset of AIH. In a study of 26 patients with recent onset AIH, only one patient had hepatitis with CN[22]. Therefore, acute onset AIH may simply be a sign of an acute exacerbation of pre-existing chronic AIH[6,22]. Indeed, Miyake *et al*[23] reported that 47 of 160 patients (29%) had CN, and found CN not only in patients with acute onset AIH, but also acute exacerbation of pre-existing chronic AIH. Another possibility is that AIH with CN represents a different form of AIH.

In this study, we observed CN in 31.7% of our AIH patients with acute presentation and the frequency of advanced fibrosis was significantly different between patients with and without CN. Serum IgG levels of patients with CN were significantly lower while ANA-negative rates were significantly higher than in patients without CN. These findings indicate that CN reflects an early lesion in AIH. Moreover, two of the three CN cases without classic histological features of AIH progressed to classic AIH. In addition, none of the patients with CN presented with liver cirrhosis at diagnosis. However, it is difficult to identify CN, as the area of zone 3 is unclear in cases of liver cirrhosis. Similarly, in a recent study of six AIH patients with CN, none presented with liver cirrhosis and only one had elevated serum IgG levels[20]. In another study, serum ALT levels were higher in patients with CN than in patients without CN, and two of 20 patients with CN had undetectable autoantibodies and normal serum IgG levels at initial presentation[7].

We also evaluated the ability of a simplified scoring system to identify AIH with and without CN compared with the revised original diagnostic criteria. Although there was no significant difference between groups evaluated using the revised original score, the simplified AIH score of patients with CN was significantly lower. Miyake *et al*[24] reported that 30% of male patients, 23% of patients with acute presentation, 50% of patients showing histological acute hepatitis and 46% of patients negative

for antinuclear antibodies at presentation who were not diagnosed with AIH according to the simplified criteria. The revised original scoring system has greater value in diagnosing patients with few or atypical features of AIH, especially in patients with cryptogenic or autoantibody-negative chronic hepatitis. However, the simplified scoring system can exclude the diagnosis more frequently in patients with etiologically distinctive disease who have concurrent immune manifestations[25,26].

On the other hand, the American Association for the Study of Liver Disease practice guidelines state that in patients with CN, sequential liver tissue examinations demonstrate transition from CN to interface hepatitis[27]. Our study indicated that 3 of 13 cases of AIH with acute presentation showed CN without portal inflammation (interface hepatitis) and 10 of 13 showed CN with portal inflammation. In addition, 26 of 41 cases of AIH with acute presentation showed portal inflammation without CN. Thus, portal inflammation with or without CN is considered to be an acute exacerbation phase of AIH. CN without portal inflammation is the most important histological finding which relates to the acute hepatitis phase of AIH. Taken together, CN is observed in both patients with acute hepatitis phase and acute exacerbation phase of AIH, although AIH with CN often shows clinical features of the genuine acute form.

COMMENTS

Background

Recently, it has been reported that there are two types of the acute presentation in patients with autoimmune hepatitis (AIH) in Japan. Typical liver histology of AIH is interface hepatitis with lymphocytic/lymphoplasmacytic infiltrates in portal tracts and extending into lobules, although centrilobular necrosis (CN) has been observed without the classic histological features of AIH.

Research frontiers

Recent reports have showed that it may be possible to distinguish the acute hepatitis phase from the acute exacerbation phase of AIH by the existence of both CN and portal inflammation.

Innovations and breakthroughs

CN is a non-specific histological finding caused by hepatotoxins, such as acetaminophen, paracetamol, thioacetamide, tetrachloride, congestive hepatic injury and cardiac hepatopathy due to acute right side cardiac failure. Other reports have highlighted that CN probably reflects early stage AIH detected primarily in patients with an acute onset.

Applications

This study may suggest a future strategy for differentiating between the acute hepatitis phase and the acute exacerbation phase of AIH based on the existence of both CN and portal inflammation.

Terminology

Confluent necrosis with inflammation in zone 3 was considered to be CN. Elevated serum alanine aminotransferase (> 5x upper limit of normal) identified acute presentation of the disease. Patients with acute presentation of the disease with histological evidence of chronic hepatitis, such as the presence of fibrosis and inflammatory cell infiltrations in the portal tracts with interface hepatitis, were diagnosed as acute exacerbation phase. Patients with acute presentation of disease with no history of any prior liver disease and no histological evidence of chronic hepatitis were diagnosed as acute hepatitis phase.

Peer review

The authors compared the clinicopathological features of acute presentation of AIH with and without CN in series of well-characterized cases affected by AIH in a single hospital in Japan. They conclude that CN is a feature both in patients with acute AIH or acute exacerbation of AIH. The study is well designed and performed. Although the number of cases is quite small, they are well-characterized so the conclusions of this study are solid and of importance.

REFERENCES

1 **Krawitt EL**. Autoimmune hepatitis. *N Engl J Med* 2006; **354**: 54-66
2 **Czaja AJ**, Freese DK. Diagnosis and treatment of autoimmune hepatitis. *Hepatology* 2002; **36**: 479-497
3 **Gardner CR**, Laskin JD, Dambach DM, Chiu H, Durham SK, Zhou P, Bruno M, Gerecke DR, Gordon MK, Laskin DL. Exaggerated hepatotoxicity of acetaminophen in mice lacking tumor necrosis factor receptor-1. Potential role of inflammatory mediators. *Toxicol Appl Pharmacol* 2003; **192**: 119-130
4 **Alison MR**, Sarraf CE. Liver cell death: patterns and mechanisms. *Gut* 1994; **35**: 577-581
5 **Myers RP**, Cerini R, Sayegh R, Moreau R, Degott C, Lebrec D, Lee SS. Cardiac hepatopathy: clinical, hemodynamic, and histologic characteristics and correlations. *Hepatology* 2003; **37**: 393-400
6 **Okano N**, Yamamoto K, Sakaguchi K, Miyake Y, Shimada N, Hakoda T, Terada R, Baba S, Suzuki T, Tsuji T. Clinicopathological features of acute-onset autoimmune hepatitis. *Hepatol Res* 2003; **25**: 263-270
7 **Hofer H**, Oesterreicher C, Wrba F, Ferenci P, Penner E. Centrilobular necrosis in autoimmune hepatitis: a histological feature associated with acute clinical presentation. *J Clin Pathol* 2006; **59**: 246-249
8 **Zen Y**, Notsumata K, Tanaka N, Nakanuma Y. Hepatic centrilobular zonal necrosis with positive antinuclear antibody: a unique subtype or early disease of autoimmune hepatitis? *Hum Pathol* 2007; **38**: 1669-1675
9 **Lefkowitch JH**, Apfelbaum TF, Weinberg L, Forester G. Acute liver biopsy lesions in early autoimmune ("lupoid") chronic active hepatitis. *Liver* 1984; **4**: 379-386
10 **Abe M**, Onji M, Kawai-Ninomiya K, Michitaka K, Matsuura B, Hiasa Y, Horiike N. Clinicopathologic features of the severe form of acute type 1 autoimmune hepatitis. *Clin Gastroenterol Hepatol* 2007; **5**: 255-258
11 **Pratt DS**, Fawaz KA, Rabson A, Dellelis R, Kaplan MM. A novel histological lesion in glucocorticoid-responsive chronic hepatitis. *Gastroenterology* 1997; **113**: 664-668
12 **Takahashi H**, Zeniya M. Acute presentation of autoimmune hepatitis: Does it exist? A published work review. *Hepatol Res* 2011; **41**: 498-504
13 **Onji M**. Proposal of autoimmune hepatitis presenting with acute hepatitis, severe hepatitis and acute liver failure. *Hepatol Res* 2011; **41**: 497
14 **Johnson PJ**, McFarlane IG. Meeting report: International Autoimmune Hepatitis Group. *Hepatology* 1993; **18**: 998-1005
15 **Alvarez F**, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, Chapman RW, Cooksley WG, Czaja AJ, Desmet VJ, Donaldson PT, Eddleston AL, Fainboim L, Heathcote J, Homberg JC, Hoofnagle JH, Kakumu S, Krawitt EL, Mackay IR, MacSween RN, Maddrey WC, Manns MP, McFarlane IG, Meyer zum Büschenfelde KH, Zeniya M. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol* 1999; **31**: 929-938
16 **Hennes EM**, Zeniya M, Czaja AJ, Parés A, Dalekos GN, Krawitt EL, Bittencourt PL, Porta G, Boberg KM, Hofer H, Bianchi FB, Shibata M, Schramm C, Eisenmann de Torres B, Galle PR, McFarlane I, Dienes HP, Lohse AW. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology* 2008; **48**: 169-176
17 **Desmet VJ**, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. *Hepatology* 1994; **19**: 1513-1520
18 **Czaja AJ**. Autoimmune liver disease. *Curr Opin Gastroenterol* 2006; **22**: 234-240
19 **Carpenter HA**, Czaja AJ. The role of histologic evaluation in

the diagnosis and management of autoimmune hepatitis and its variants. *Clin Liver Dis* 2002; **6**: 685-705
20 **Czaja AJ**, Bayraktar Y. Non-classical phenotypes of autoimmune hepatitis and advances in diagnosis and treatment. *World J Gastroenterol* 2009; **15**: 2314-2328
21 **Misdraji J**, Thiim M, Graeme-Cook FM. Autoimmune hepatitis with centrilobular necrosis. *Am J Surg Pathol* 2004; **28**: 471-478
22 **Burgart LJ**, Batts KP, Ludwig J, Nikias GA, Czaja AJ. Recent-onset autoimmune hepatitis. Biopsy findings and clinical correlations. *Am J Surg Pathol* 1995; **19**: 699-708
23 **Miyake Y**, Iwasaki Y, Terada R, Onishi T, Okamoto R, Takaguchi K, Ikeda H, Makino Y, Kobashi H, Sakaguchi K, Shiratori Y. Clinical features of Japanese type 1 autoimmune hepatitis patients with zone III necrosis. *Hepatol Res* 2007; **37**: 801-805
24 **Miyake Y**, Iwasaki Y, Kobashi H, Yasunaka T, Ikeda F, Takaki A, Yamamoto K. Clinical features of autoimmune hepatitis diagnosed based on simplified criteria of the International Autoimmune Hepatitis Group. *Dig Liver Dis* 2010; **42**: 210-215
25 **Czaja AJ**. Performance parameters of the diagnostic scoring systems for autoimmune hepatitis. *Hepatology* 2008; **48**: 1540-1548
26 **Czaja AJ**, Manns MP. Advances in the diagnosis, pathogenesis, and management of autoimmune hepatitis. *Gastroenterology* 2010; **139**: 58-72.e4
27 **Manns MP**, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, Vierling JM. Diagnosis and management of autoimmune hepatitis. *Hepatology* 2010; **51**: 2193-2213

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BRIEF ARTICLE

Variceal hemorrhage: Saudi tertiary center experience of clinical presentations, complications and mortality

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Abstract

AIM: To determine the clinical presentation, underlying etiology and short- and long-term outcomes of acute variceal bleeding (AVB).

METHODS: A retrospective descriptive cohort study of cirrhotic patients with AVB who were admitted to King Abdul Aziz University Hospital between January 2005 and December 2009. We obtained demographic data for all patients. For each patient we also obtained the clinical data at presentation; cause of liver cirrhosis, bleeding presentation (hematemesis and/or melena), presence of ascites, hepatic encephalopathy and renal impairment (RI) or hepatorenal syndrome. We carried out complete blood count, prothrombin time evaluation, and liver function tests. We also report all episodes of re-bleeding after the first episode of AVB, both during the initial admission and after discharge. We recorded the length of stay for each patient and thereby calculated the mean duration of stay for all patients. The length of follow-up after the first AVB and the outcome for each patient at the end of the study period were recorded. Causes of mortality either related to liver disease or non-liver disease cause were determined.

RESULTS: A 125 patients were enrolled in the study. The number of episodes of AVB for each patients varied between 1 and 10. Survival from the first attack of AVB to death was 20.38 mo (SD 30.86), while the length of follow-up for the living patients was 53.58 mo (SD 24.94). Total number of AVB admissions was 241. Chronic hepatitis C, the commonest underlying etiology for liver disease, was present in 46 (36.8%) patients. Only 35 (28%) patients had received a primary prophylactic β-blocker before the first bleeding episode. The mean hemoglobin level at the time of admission was 8.59 g/dL (SD 2.53). Most patients had Child-Pugh Class C 41 (32.8%) or Class B 72 (57.6%) disease. Hematemesis was the predominant symptom and was found in 119 (95.2%) patients, followed by melena in 75 (60.0%) patients. Ascites of variable extent was documented in 93 (74.4%) patients. We identified hepatic encephalopathy in 31 (28.8%) patients and spontaneous bacterial peritonitis in 17 (13.6%). Bleeding gastric varices was the cause of AVB in 2 patients. AVB was associated with shock in 22 patients, 13 of whom (59.1%) had Child-Pugh class C disease. RI was noted in 19 (46.3%) of 41 patients in Child-Pugh class C and 14 (19.4%) of 72 patients in Child-Pugh class B. None of the patients with Child-Pugh class A disease had RI. Emergency endoscopy was effective in controlling the bleeding, although the re-bleeding rate was still high, 12 (9.6%) during the same admission and 55 (44%) after discharge. The re-bleeding rate was higher in patients with ascites, occurring in 40/55 (72.2%). The length of hospital stay was 1-54 d with a mean of 8.7 d. Three patients had emergency surgery due to failure of endoscopic treatment and balloon tamponade. The overall long term mortality was 65%. Survival from the first attack of AVB to death was 20.38 ± 30.86 mo, while the length of follow-up for the living patients was 53.58 ± 24.94 mo. Patients with Child-Pugh score C had a higher risk of liver disease-related mortality

(67.6%). RI (developed during admission) was the main factor that was associated with mortality (P = 0.045).

CONCLUSION: The majority of patients with liver disease who present at the emergency unit for AVB are at an advanced stage of the disease. The outcome is poorer for patients who develop RI during hospitalization.

Key words: Endoscopy; Liver disease; Mortality; Outcome; Varices; Variceal bleeding

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INTRODUCTION

Variceal bleeding is a leading cause of mortality and morbidity in patients with liver cirrhosis of various causes[1]. Varices and variceal bleeding can develop during both the early or late stages of cirrhosis (from Child-Pugh A to C)[2]. It has been reported that about half of cirrhotic patients will develop varices due to portal hypertension and 40% of them will have variceal bleeding[3,4]. A variety of non-invasive factors have been linked to the development of varices in cirrhotic patients. These include platelet counts, portal vein diameter, the size of the spleen and aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio[5-7]. Similarly, several reports have addressed the use of non-invasive parameters to predict the presence of large esophageal varices with a high chance of bleeding. Those parameters most frequently include low platelet counts, splenomegaly, prothrombin time, ascites and advanced Child-Pugh class[8-11].

The gold standard test for the diagnosis of varices is upper gastrointestinal endoscopic examination (OGD). Hence, routine screening by OGD is recommended for all cirrhotic patients[12]. Once large varices are diagnosed, primary prophylactic measures for prevention of the first bleeding episode are recommended[12]. Selective β-blockers such as propranolol have been the most frequently used and studied agents for medical primary prophylaxis[12,13]. Variceal band ligation has been also used as prophylaxis for the prevention of variceal bleeding, and shows less frequent bleeding episodes than medical prophylaxis. However, there is no significant difference in mortality[14,15].

In Saudi Arabia, only a few studies have reported the clinical outcomes of patients with acute variceal bleeding (AVB)[16-18]. In this retrospective analysis, we reviewed the medical data of patients with AVB who were admitted to King Abdul Aziz University Hospital (KAUH), Jeddah, Saudi Arabia, to determine the clinical presentation, common underlying etiology and short- and long-term outcomes of the bleeding in this group of patients.

MATERIALS AND METHODS

Study population

We conducted a retrospective descriptive cohort study of all patients with upper gastrointestinal bleeding due to AVB who were admitted to KAUH, Jeddah, Saudi Arabia between January 2005 and December 2009. Ethical approval for the study was granted by the Biomedical Ethics Research Committee of King Abdul Aziz University.

We included all patients with AVB due to underlying liver cirrhosis who had undergone emergency endoscopic intervention. We excluded elective admission episodes for variceal band ligation after acute bleeding in the same patients. For all cases included in the study, we collected the following information: age, gender, nationality, use of a primary prophylactic β-blocker (propranolol) before the first episode of variceal bleeding, clinical data on the first episode of AVB, cause of liver disease, presence of hematemesis and/or melena and the duration of symptoms. We also recorded the presence of ascites (whether none, mild, moderate or massive) and evidence of spontaneous bacterial peritonitis (SBP), as reflected by fever and abdominal pain and ascitic fluid analysis for cell count. The presence of hepatic encephalopathy on admission was also noted. We looked for the presence of hemodynamic instability by measuring blood pressure and pulse rate at the time of presentation to the emergency department. For patients who had more than one episode of AVB, we recorded the number of episodes.

We conducted the following laboratory tests: complete blood count at the time of admission; prothrombin time to assess the Child-Pugh score on admission; and liver function tests, namely serum ALT, AST, alkaline phosphatase, γ-glutamyl transferase, total protein, albumin, total and direct bilirubin. Our management for all patients with AVB includes standard resuscitation measures in addition to the use of intravenous vasoconstrictors, such as Octreotide, followed by endoscopic therapy. In patients who had severe acute bleeding that obscured the field and caused failure of immediate band ligation, balloon tamponade was used and endoscopic banding was then performed within the next 48 h. In addition to this, and as per the American Association for the Study of Liver Diseases recommendation, all patients managed for AVB at our institution receive short-term prophylactic antibiotics during hospitalization[2].

The presence of renal impairment (RI) or hepatorenal syndrome at presentation or during admission for

AVB was recorded. We define in-hospital re-bleeding as recurrence of variceal bleeding during the admission after initial control and late re-bleeding- as recurrent variceal bleeding between 6 wk and 6 mo after discharge from the hospital. The length of hospital stay for each patient during the admission was also recorded. The duration of follow-up after the first episode of variceal bleeding and the outcome of each patient at the end of the study period were recorded. The cause of mortality during the follow up was noted as being due to either liver disease or non-liver disease.

Statistical analysis

We performed statistical analysis using the SPSS Version 15. χ^2 test was used to assess the relation between the Child-Pugh score and the risk of bleeding and mortality. The relation between the severity of bleeding and the Child-Pugh score was also assessed by the χ^2 test. Descriptive statistics was used to determine mortality. Multivariate analysis was used to assess the risk factors associated with mortality.

RESULTS

Baseline characteristics

One hundred twenty-five patients were enrolled in the study. The number of admissions was 1-10 per patient with a total of 241 admissions (Table 1). Only 35 (28.0%) patients had a history of β-blocker use. Ten (8.0%) had Child-Pugh class A disease, 72 (57.6%) had Child-Pugh class B, and 41 (32.8%) had Child-Pugh class C. The Child-Pugh score was not determined for 2 patients. Patients in Child-Pugh class A had no previous evidence of liver cirrhosis. The most common cause of liver disease was chronic hepatitis C (n = 46, 36.8%) followed by non alcoholic fatty liver disease (n = 26, 20.8%). For six patients, the cause of liver disease was not determined during admission and the patients were lost to follow up after the initial admission. Hematemesis was a presenting symptom in the majority of the cases (n = 119, 95.2%), while melena was noted in 75 (60.0%) patients. Fever was uncommon, noted in 15 (12.0%) of the patients, and abdominal pain was seen in only 13 (10.4%) of the cases. The presence or absence of ascites was documented in 123 patients. There was no ascites in 30 (24.0%) patients, 46 (36.8%) had mild ascites, 32 (25.6%) had moderate ascites and 15 (12%) had massive ascites. Hepatic encephalopathy was present in 31 (24.8%) patients on admission, and SBP was diagnosed in 17 (13.6%) patients.

The results of baseline laboratory investigations are summarized in (Table 2). All patients from our cohort underwent diagnostic and therapeutic emergency endoscopy within 12 h of admission after the baseline standard measures for AVB. Two patients who had bleeding gastric varices had optimal response to cyanoacrylate injection.

Relationship between the clinical variables

The bleeding was more severe in patients with ascites; 20 (90.9%) of 22 patients who had shock at presentation had ascites. Thirteen (59.1%) of these 22 were Child-Pugh C. Thirty-three (26.4%) patients developed RI during hospitalization. Amongst the patients in Child-Pugh class C, 19 of 41 patients (46.3%) developed renal failure. RI was noted in 14 (19.4%) of 72 patients in Child-Pugh class B, while no case of renal failure was observed in patients in Child-Pugh class A. Based on the degree of ascites, RI was noted in 11 patients with massive ascites, in 9 patients with moderate ascites, and in 10 patients with mild ascites. Only 3 patients without ascites developed RI. In-hospital re-bleeding was recorded in 12 (9.6%) patients and late re-bleeding in 55 (44.0%) patients. Patients who had ascites were more likely to have a re-bleeding episode; they accounted for 40 of 55 (72.2%) patients with re-bleeding.

Table 1 Number of emergency admissions *n* (%)

No. of episodes of acute variceal bleeding	No. of patients
1	70 (56.0)
2	27 (21.6)
3	15 (12.0)
4	5 (4.0)
5	1 (0.8)
6	5 (4.0)
7	1 (0.8)
10	1 (0.8)
Total	125 (100)

Relationship between the length of hospital stay and severity of ascites and renal failure

The length of hospital stay varied between 1 and 54 d (mean ± SD, 8.7 ± 7.9 d). Length of stay was longer for patients who had massive ascites when compared with those who had mild, moderate or no ascites, but the difference was only statistically significant between patients with massive ascites and those with mild ascites (P = 0.036).

Three patients had emergency devascularization surgery for refractory variceal bleeding; one of them had a huge gastric varix.

Survival and mortality

The survival period from the first attack of AVB to death was 20.38 ± 30.86 mo. The length of follow-up for the living patients was 53.58 ± 24.94 mo. Amongst the 60 patients who were available for follow up, 37 (61.7%) died from complications due to liver disease after a mean of 20.38 ± 30.86 mo, while the cause of death was unrelated to the underlying liver disease in 2 (3.3%) cases. The overall mortality was 65%. Patients with Child-Pugh score C had a higher risk of liver disease-related mortality. Twenty-five (67.6%) of the 37 patients who died were Child-Pugh class C. Patients who had ascites also had a higher risk of mortality related to liver disease; 34 of 37 (91.9%). Four of the patients who had SBP were lost to follow-up, while 11 of the remaining 13 patients died of

Table 2 Mean and SD of the laboratory results of all patients at the time of first admission

Investigation	Minimum	Maximum	mean (SD)	Reference range
CBC				
White cell count (K/μL)	1.8	28.10	8.27 (5.12)	3-11
Hemoglobin (g/dL)	1.0	15.70	8.59 (2.53)	12-17
Platelets (K/μL)	24.0	463.00	133.89 (85.63)	100-400
ALT (U/L)	13.0	759.0	75.73 (84.93)	30-65
AST (U/L)	12.0	631.0	90.62 (106.2)	15-37
Albumin (g/L)	10.0	37.0	24.71 (5.88)	35-50
Bilirubin (μmol/L)	5.0	473.0	37.12 (51.82)	0-17
Alkaline phosphate (U/L)	17.0	561.0	141.31 (83.10)	50-136
GGT (U/L)	14.0	889.0	132.03 (143.48)	5-85
Total protein (g/L)	40.0	87.0	64.37 (10.95)	64-82
Prothrombin time (s)	11.2	141.0	18.86 (14.80)	10-14

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CBC: Complete blood count; GGT: γ glutamyl trasferase.

liver disease. On multiple regression analysis, RI (developed during admission) was the only factor that was significantly associated with mortality ($P = 0.045$).

Mortality during the first admission was reported in 19 (15.2%) patients, all the remaining patients had follow-up elective band ligation at 3-4 wk intervals until eradication of the varices was achieved [21 patients (16.8%)] or until the patient died [20 (16%)] or lost from the follow-up [65 (52%)].

DISCUSSION

The results of this study show that chronic hepatitis C was the most common cause of liver disease in patients who presented with AVB at the emergency department of KAUH. On admission, the majority of the patients were in Child-Pugh class B and C, and severe variceal bleeding was greater in patients with advanced disease (Child-Pugh class C). Mortality was related to the underlying cause of the disease in 37 of 39 patients who died, while the cause was not related to the underlying liver disease in the remaining two patients. RI, developed during the course of hospitalization, was the only factor that was significantly associated with mortality.

Hematemesis was the presenting symptom in up to 95.2% of our study population. Melena was present in 50.0%, while abdominal pain was an infrequent symptom, observed in only 10.4% of the cases. It was reported that many patients with large varices are asymptomatic, and variceal rupture with massive upper gastrointestinal hemorrhage can sometimes be the first presenting symptom in patients with liver cirrhosis[19]. This was probably the case in patients with stable Child-Pugh class A disease from our cohort. On the other hand, patients with advanced liver disease and Child-Pugh class C have a higher risk of variceal bleeding and poorer outcome compared with patients who have Child-Pugh class A disease and compensated cirrhosis[19], as was the case in our study.

The main factor that predicts the severity of variceal bleeding is intravariceal pressure, and the level of bleeding could vary from moderate to life-threatening massive hemorrhage with shock[20,21]. Ascites has been reported as a predictor of the severity of AVB[22]. The fact that the bleeding was more severe in our patients with ascites could be due to an elevated portal vein pressure as a result of increased intra-abdominal pressure.

The initial management of AVB includes standard resuscitation measures in addition to the use of intravenous vasoconstrictors, such as Octreotide, followed by endoscopic therapy[20-24]. This will control the bleeding in the majority of patients. However, in cases where the bleeding is not controlled by initial measures, emergency transjugular intrahepatic portosystemic shunt is the best alternative in those who can tolerate the procedure[20,21,23]. Only 3 of our patients had emergency surgery for refractory variceal bleeding. Immediate liver transplantation may be considered if possible in appropriate candidates[21,23,25]. Repeated endoscopic management until complete obliteration is achieved is recommended for patients who responded to this procedure[20,21]. The addition of β-blockers as secondary prophylaxis has been shown in several reports to be superior to the use endoscopic management alone[21,26]. All of our patients had β-blockers as secondary prophylaxis and none of them experienced serious side effects. In cases of acute gastric variceal bleeding, cyanoacrylate injection has been also tried for secondary prophylaxis and shown to be superior to β-blockers[27]. It was used effectively in two patients from our cohort who had gastric varices. New modalities for secondary prevention of re-bleeding, including microwave coagulation, have also been studied and shown to be effective[26].

In this study, in-hospital re-bleeding was observed in about 9.6% of the cases while nearly half of the patients had recurrent variceal bleeding after discharge. Other authors reported a similar rate of early re-bleeding in patients who underwent endoscopic therapy for AVB. The rate of re-bleeding in their study was between 9% and 19%[28]. In a recent study, the authors found that the predictors of early re-bleeding were moderate to excessive ascites, the number of bands placed during endoscopic band ligation, the extent of varices, and the prothrombin time. They went further and demonstrated that a moderate to excessive volume of ascites was the most impor-

tant factor predicting variceal bleeding following endoscopic variceal ligation[29]. Other factors that have been associated with high mortality and re-bleeding following AVB are the presence of hepatocellular carcinoma and bacterial infection at the time of bleeding[29,30].

The overall mortality in this study was 65%, higher than the 19% reported by other authors in a large study conducted at a tertiary hospital in Riyadh[18]. In other studies conducted abroad, the rate of mortality is at least 20% at 6 wk in patients with AVB[31,32]. The high mortality rate in our study could be related to the presence of advanced liver disease in many patients. We found that patients in Child-Pugh class C, SBP and ascites presented a higher risk of dying due to liver disease, although RI, developed during hospitalization, was the sole factor that was significantly related to mortality.

In conclusion, most patients with liver disease that present at the emergency unit for AVB are at an advanced stage of the disease. Endoscopy is a reliable method to control the bleeding, but it is associated with a high rate of late re-bleeding. Hence, close follow up is necessary in patients who have undergone this procedure for bleeding varices. The outcome is poorer for patients who develop RI during hospitalization, and the principal of clinicians should not be on the bleeding alone but measures should also be taken to prevent the occurrence of complications during hospitalization. Emphasis on endoscopic screening of patients who have liver cirrhosis for the presence of varices and early implementation of primary prophylaxis will help to reduce the chance of variceal bleeding and its complications.

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COMMENTS

Background

Acute variceal bleeding (AVB) is a major cause of morbidity and mortality in patient with liver cirrhosis. About half of cirrhotic patients especially those with advance disease will develop esophageal varices and variceal bleeding. Researchers and experts from different regions of the world have been working to improve therapeutic techniques and medical care practice in AVB to achieve better outcomes. Similarly the world major associations for liver disease are continuously updating the clinical data and practice guideline for the management of AVB. However there are only limited data from the Middle East and Arab world in this field. Hence, studies from this part of the world will reflect the local clinical data and outcomes of such patients and may show possible differences from other international figures.

Research frontiers

The focus of this clinical study was to define the clinical outcomes, complications and mortality risk factors of acute variceal hemorrhage at King Abdul Aziz University (KAUH) hospital, a major teaching hospital and tertiary care center in the region. KAUH receives large numbers both Saudi and non-Saudi patients

Innovations and breakthroughs

Most breakthroughs in AVB have been in the field of AVB management. Several international guidelines have been suggested by major liver associations, such as American Association for the Study of Liver Diseases (http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/Prevention%20and%20Management%20of%20Gastro%20Varices%20and%20Hemorrhage.pdf), EASL and the APASL. The introduction of TIPS and early surgical intervention in the management of variceal bleeding has led to significant improvement in patient outcomes.

Applications

The study has shown that development of renal impairment or hepatorenal syndrome are associated with a high chance of mortality. Future prospective studies on similar patients with early initiation of preventive measures for renal failure, such as albumin infusion with or without terlipressin, might lead to reduction in the mortality rate of patients with AVB.

Peer review

The manuscript describes the outcomes of variceal bleeding and band ligation in a series of 125 patients. A variety of outcomes and parameters are described. Only 50% of patients were followed up for mortality analysis and this seems to be more the case for patients in Childs C than other patients.

REFERENCES

1 **Gado AS**, Ebeid BA, Abdelmohsen AM, Axon AT. Clinical outcome of acute upper gastrointestinal hemorrhage among patients admitted to a government hospital in Egypt. *Saudi J Gastroenterol* 2012; **18**: 34-39
2 **Garcia-Tsao G**, Sanyal AJ, Grace ND, Carey W. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology* 2007; **46**: 922-938
3 **Toubia N**, Sanyal AJ. Portal hypertension and variceal hemorrhage. *Med Clin North Am* 2008; **92**: 551-574, viii
4 **Merli M**, Nicolini G, Angeloni S, Rinaldi V, De Santis A, Merkel C, Attili AF, Riggio O. Incidence and natural history of small esophageal varices in cirrhotic patients. *J Hepatol* 2003; **38**: 266-272
5 **Hong WD**, Zhu QH, Huang ZM, Chen XR, Jiang ZC, Xu SH, Jin K. Predictors of esophageal varices in patients with HBV-related cirrhosis: a retrospective study. *BMC Gastroenterol* 2009; **9**: 11
6 **Giannini E**, Botta F, Borro P, Risso D, Romagnoli P, Fasoli A, Mele MR, Testa E, Mansi C, Savarino V, Testa R. Platelet count/spleen diameter ratio: proposal and validation of a non-invasive parameter to predict the presence of oesophageal varices in patients with liver cirrhosis. *Gut* 2003; **52**: 1200-1205
7 **Prihatini J**, Lesmana LA, Manan C, Gani RA. Detection of esophageal varices in liver cirrhosis using non-invasive parameters. *Acta Med Indones* 2005; **37**: 126-131
8 **Chang MH**, Sohn JH, Kim TY, Son BK, Kim JP, Jeon YC, Han DS. [Non-endoscopic predictors of large esophageal varices in patients with liver cirrhosis]. *Korean J Gastroenterol* 2007; **49**: 376-383
9 **Sharma SK**, Aggarwal R. Prediction of large esophageal varices in patients with cirrhosis of the liver using clinical, laboratory and imaging parameters. *J Gastroenterol Hepatol* 2007; **22**: 1909-1915
10 **Sarangapani A**, Shanmugam C, Kalyanasundaram M, Rangachari B, Thangavelu P, Subbarayan JK. Noninvasive prediction of large esophageal varices in chronic liver disease patients. *Saudi J Gastroenterol* 2010; **16**: 38-42
11 **Thabut D**, Trabut JB, Massard J, Rudler M, Muntenau M, Messous D, Poynard T. Non-invasive diagnosis of large oesophageal varices with FibroTest in patients with cirrhosis: a preliminary retrospective study. *Liver Int* 2006; **26**: 271-278
12 **Garcia-Tsao G**, Bosch J, Groszmann RJ. Portal hypertension and variceal bleeding--unresolved issues. Summary of an American Association for the study of liver diseases and European Association for the study of the liver single-topic conference. *Hepatology* 2008; **47**: 1764-1772
13 **Abraczinskas DR**, Ookubo R, Grace ND, Groszmann RJ, Bosch J, Garcia-Tsao G, Richardson CR, Matloff DS, Rodés J, Conn HO. Propranolol for the prevention of first esophageal

variceal hemorrhage: a lifetime commitment? *Hepatology* 2001; **34**: 1096-1102
14 **Khuroo MS**, Khuroo NS, Farahat KL, Khuroo YS, Sofi AA, Dahab ST. Meta-analysis: endoscopic variceal ligation for primary prophylaxis of oesophageal variceal bleeding. *Aliment Pharmacol Ther* 2005; **21**: 347-361
15 **Tripathi D**, Ferguson JW, Kochar N, Leithead JA, Therapondos G, McAvoy NC, Stanley AJ, Forrest EH, Hislop WS, Mills PR, Hayes PC. Randomized controlled trial of carvedilol versus variceal band ligation for the prevention of the first variceal bleed. *Hepatology* 2009; **50**: 825-833
16 **Al-Rashed RS**, Laajam MA, Mofleh IA, Al-Aska AK, Al-Faleh FZ, Hussein J. Acute upper gastrointestinal bleeding in King Khalid University Hospital. *Ann Saudi Med* 1990; **10**: 110A
17 **Ahmed ME**, al-Knaway B, al-Wabel AH, Malik GM, Foli AK. Acute upper gastrointestinal bleeding in southern Saudi Arabia. *J R Coll Physicians Lond* 1997; **31**: 62-64
18 **Alam MK**. Factors affecting hospital mortality in acute upper gastrointestinal bleeding. *Saudi J Gastroenterol* 2000; **6**: 87-91
19 **Silkauskaite V**, Pranculis A, Mitraite D, Jonaitis L, Petrenkiene V, Kupcinskas L. Hepatic venous pressure gradient measurement in patients with liver cirrhosis: a correlation with disease severity and variceal bleeding. *Medicina* (Kaunas) 2009; **45**: 8-13
20 **Sarin SK**, Kumar A. Gastric varices: profile, classification, and management. *Am J Gastroenterol* 1989; **84**: 1244-1249
21 **Abbasi A**, Bhutto AR, Butt N, Munir SM, Dhillo AK. Frequency of portal hypertensive gastropathy and its relationship with biochemical, haematological and endoscopic features in cirrhosis. *J Coll Physicians Surg Pak* 2011; **21**: 723-726
22 **Sarin SK**, Kumar A, Angus PW, Baijal SS, Baik SK, Bayraktar Y, Chawla YK, Choudhuri G, Chung JW, de Franchis R, de Silva HJ, Garg H, Garg PK, Helmy A, Hou MC, Jafri W, Jia JD, Lau GK, Li CZ, Lui HF, Maruyama H, Pandey CM, Puri AS, Rerknimitr R, Sahni P, Saraya A, Sharma BC, Sharma P, Shiha G, Sollano JD, Wu J, Xu RY, Yachha SK, Zhang C. Diagnosis and management of acute variceal bleeding: Asian Pacific Association for Study of the Liver recommendations. *Hepatol Int* 2011; **5**: 607-624
23 **Lo GH**. Management of acute esophageal variceal hemorrhage. *Kaohsiung J Med Sci* 2010; **26**: 55-67
24 **Sharma P**, Sarin SK. Improved survival with the patients with variceal bleed. *Int J Hepatol* 2011; **2011**: 356919
25 **Orloff MJ**, Isenberg JI, Wheeler HO, Haynes KS, Jinich-Brook H, Rapier R, Vaida F, Hye RJ. Randomized trial of emergency endoscopic sclerotherapy versus emergency portacaval shunt for acutely bleeding esophageal varices in cirrhosis. *J Am Coll Surg* 2009; **209**: 25-40
26 **Funakoshi N**, Ségalas-Largey F, Duny Y, Oberti F, Valats JC, Bismuth M, Daurès JP, Blanc P. Benefit of combination β-blocker and endoscopic treatment to prevent variceal rebleeding: a meta-analysis. *World J Gastroenterol* 2010; **16**: 5982-5992
27 **Mishra SR**, Chander Sharma B, Kumar A, Sarin SK. Endoscopic cyanoacrylate injection versus beta-blocker for secondary prophylaxis of gastric variceal bleed: a randomised controlled trial. *Gut* 2010; **59**: 729-735
28 **Lo GH**, Chen WC, Chen MH, Lin CP, Lo CC, Hsu PI, Cheng JS, Lai KH. Endoscopic ligation vs. nadolol in the prevention of first variceal bleeding in patients with cirrhosis. *Gastrointest Endosc* 2004; **59**: 333-338
29 **Xu L**, Ji F, Xu QW, Zhang MQ. Risk factors for predicting early variceal rebleeding after endoscopic variceal ligation. *World J Gastroenterol* 2011; **17**: 3347-3352
30 **Sempere L**, Palazón JM, Sánchez-Payá J, Pascual S, de Madaria E, Poveda MJ, Carnicer F, Zapater P, Pérez-Mateo M. Assessing the short- and long-term prognosis of patients with cirrhosis and acute variceal bleeding. *Rev Esp Enferm Dig* 2009; **101**: 236-248
31 **Carbonell N**, Pauwels A, Serfaty L, Fourdan O, Lévy VG, Poupon R. Improved survival after variceal bleeding in patients with cirrhosis over the past two decades. *Hepatology* 2004; **40**: 652-659
32 **D'Amico G**, De Franchis R. Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. *Hepatology* 2003; **38**: 599-612

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AHPBA Sponsored Consensus Conference on the Multidisciplinary Treatment of Colorectal Cancer Liver Metastases
San Francisco, CA, United States

January 20-21, 2012
AGA Clinical Congress of Gastroenterology and Hepatology: Practice, Evidence and Quality in 2012
Miami, FL, United States

January 27-28, 2012
28th Annual Meeting of the German Association for the Study of the Liver
Hamburg, Germany

January 30-31, 2012
5th International Conference on the Management of Patients with Viral Hepatitis
Paris, France

February 8-10, 2012
Stockholm Liver Week 2012
Stockholm, Sweden

February 16-19, 2012
22nd Conference of the Asian Pacific Association for the Study of the Liver
Taipei, Taiwan, China

March 16 -17, 2012
Hepatitis Single Topic Conference
Atlanta, GA, United States

March 16-17, 2012
ESGE - Workshop on Advanced Endoscopy with Live Demonstrations
Vienna, Austria

March 31-April 1, 2012
27th Annual New Treatments in Chronic Liver Disease
San Diego, CA, United States

April 18-22, 2012
The International Liver Congress by EASL
Barcelona, Spain

April 27-28, 2012
The European Society for Paediatric Gastroenterology, Hepatology and Nutrition
Stockholm, Sweden

May 16-19, 2012
International Liver Transplant Society 18th Annual International Congress 2012
San Francisco, CA, United States

May 19-22, 2012
Digestive Disease Week 2012
San Diego, CA, United States

June 22-23, 2012
EASL Monothematic Conference: Vascular Liver Diseases
Tallin, Estonia

July 1-5, 2012
10th World Congress of the International Hepato-Pancreato-Biliary Association 2012
Paris, France

September 5-8, 2012
International Congress of Pediatric Hepatology, Gastroenterology and Nutrition
Sharm El-Sheikh, Egypt

September 7-9, 2012
Viral Hepatitis Congress 2012
Macclesfield, United Kingdom

September 7-9, 2012
The Viral Hepatitis Congress
Frankfurt, Germany

September 14-16, 2012
The International Liver Cancer Association's 6th Annual Conference
Berlin, Germany

September 20-22, 2012
Prague Hepatology Meeting 2012
Prague, Czech Republic

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1st World Congress on Controversies in the Management of Viral Hepatitis
Prague, Czech Republic

October 18-20, 2012
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Berlin, Germany

November 9-13, 2012
AASLD - The Liver Meeting 2012
Boston, MA, United States

November 9-13, 2012
The Liver Meeting - 63rd Annual Meeting and Postgraduate Course of the American Association for the Study of Liver Diseases
Boston, MA, United States

November 14-18, 2012
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In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1,274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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