Alcoholic Liver Disease

***Aswad Al-Obeidy FICMS GE&H) CABM ** Makki H. Fayadh MRCP-FRCP**
***** Rayadh A. Zaidan FICS(GE&H) CABM****Ali Abdul Hamied FICS(GE&H) CABM**
******* Salah Aldeen Abdulnabi M.B, Ch.B D.M C.A.B.M**

Abstract

Background:

Alcohol remains the single most significant cause of liver disease throughout the Western world, responsible for between 40 and 80% of cases of cirrhosis in different countries. Many of the factors underlying the development of alcoholic liver injury remain unknown, and significant questions remain about the value of even very basic therapeutic strategies.

Patients and Methods: **In a cross sectional and prospective study, 113 alcoholic patients with evidence of liver disease, attending the Gastoenterorology and Hepatology teaching hospital between December 2001 and December 2003 were studied for:**

1. The clinical and biochemical spectrum of alcoholic liver disease (ALD).
2. The prevalence of HBV and HCV and its influence on the progression of ALD and hepatocellular carcinoma (HCC).
3. Alfa fetoprotein (AFP) and gamma glutamyl transpeptidase alteration.
4. The value of CAGE questionnaire in the diagnosis of alcoholism.
5. LT-RT portal vein (PV) ratio in sonographic diagnosis of ALD.
6. The value of prednisolone therapy according to the discriminant function.

Results:

The most common clinical manifestations were jaundice (62.8%) and hepatomegaly (71%). The GGT was commonly elevated irrespective of liver damage. AFP was bellow normal in (80%) and is negatively correlated with the severity of ALD.

The prevalence of HBV was (17.5%) and HCV (11.5%). The prevalence of HCC was 4.6%, 6.8% and 19.2% in mild, moderate and severe disease respectively and is significantly correlated with HCV and HBV.The majority(82%) score two and more in CAGE questionnaire. The LT-RT PV ratio equal to one and more was significantly correlated with ALD.There were significant improvement in survival rate at one year in patients with discriminant function (DF) > 32 who treated with prednisolone compared to those who received coventional treatment.

Conclusion:

The most common clinical manifestations of ALD were jaundice and hepatomegaly. The GGT was commonly elevated irrespective of liver damage. AFP was bellow normal in the majority and is negatively correlated with the severity of ALD. The HBV and HCV were fairly prevalent and were significantly correlated with the severity of ALD and HCC.The CAGE questionnaire was sensitive in the diagnosis of ALD. The LT-RT PV ratio equal to one or more was valid in sonographgic diagnosis of ALD. Glucocorticoid was effective in reducing mortality at one year in patients with discrimnant function >32.

Key wards:

Alcoholic liver disease**,** hepatocellular carcinoma, and discriminant function.

***Dr.Aswad Al-Obeidy , the Gastroenterology and Hepatology teaching hospital,Baghdad**
****Dr.Makki H. Fayadh, the Gastroenterology and Hepatology teaching hospital,Baghdad**
*****Dr.Rayadh A. Zaidan, the Gastroenterology and Hepatology teaching hospital,Baghdad**
******Dr. Ali Abdul Hamied, the Gastroenterology and Hepatology teaching hospital,Baghdad**
******* Dr. Salah Aldeen Abdulnabi ,the Gastroenterology and Hepatology Teaching hospital, Baghdad.**

Introduction:

The incidence of cirrhosis among alcoholics is about 10-15 %[1], require 80 gm of ethanol daily for 10-20yrs. Cofactors in the development of alcoholic liver disease (ALD) include: inherited differences in ethanol metabolism [2], female gender [4], coexistence of hepatitis C and B virus infection [4], malnutrition [6], obesity [6], H pylori infection and gastritis [7], concurrent exposure to hepatotoxins, cigarette smoking [8] and iron overload [9].

There are currently four major theories concerning the mechanism by which alcohol damage the liver: (1) Centrilobular hypoxia [10]. (2) Neutrophil infiltration and activation [11]. (3) Inflammatory cell infiltration and activation (kupffer cells). [12] (4) Antigenic adduct formation. [13].

The laboratory parameters that are most useful in predicting the severity of alcoholic liver injury are bilirubin level, prothrombin time (PT), and albumin level. The first two have been used to formulate a discrimination function (DF), defined as 4.6 x (PT-control in second) +bilirubin (mg/dL); when the result is greater than 32, a mortality rate of 50% can be predicted within one month [14]. The mainstays of treatment for ALD are1.Abstinence.2.Nutritional Supplement.3.Anti-inflammatory drugs. (Glucocorticoids) 4. Antioxidants. 5.Liver Transplantat. The prognosis of patient with alcoholic liver disease (ALD) depends upon several variables including the clinical severity of liver injury at diagnosis, the extent of irreversible liver damage at diagnosis and the subsequent drinking behavior. Patient with fatty liver or equivalent have had the best outcome (70% to 80% survival rate at 4 to 5 years); those with alcoholic hepatitis or cirrhosis, an intermediate outcome (50% to 75% survival rate at 4 to 5 years); and those with cirrhosis combined with alcoholic hepatitis, the worst outcome (30% to 50% survival rate at 4 to 5 years) [15].

Patients and Methods:

A total number of 113 patients with ALD attending the Gastroenterology and Hepatology teaching hospital were studied. The inclusion criteria are consumption of 80 grams of ethanol or its equivalent for 10-20 years with evidence of liver disease. Each patient was interviewed, detailed history, general medical examination was done and a study protocol paper was filled. CAGE questionnaire applied, which consists of four questions, referred to events occurring within the patient life: C Have you feel the need to cut down. A Annoyed at the suggestion of drinking problems. G Guilty of excess drinking. E Drink (Eye opener) in the morning. Score 1 point for each positive response, score of 2 or more suggest alcohol-related problem. Esophagogastroduodonoscopy (EGD) and abdominal ultrasanography to determine the of the liver, the presence of any mass and the ratio of the left to right portal vein (PV) were done compared with 50 healthy control and 50 pts with comparable CLD due to other causes. Blood sample was taken for liver function test, serum iron, total iron binding capacity (TIBC), serum ferritin, serum copper, ceruloplasmin, and lipid profile, virological and immune markers. The DF was calculated for each patient and those with DF > 32 divided into 2 groups one (10 pts) given prednisolone tab. 40 mg for 1 month and tapered over 1 month, the second group (21 pts) received only conventional treatment because of pt intolerance, compliance, doctor preference and both followed for more than a year.

The Aim of the study:

1. The clinical and biochemical spectrum of ALD.
2. The prevalence of hepatitis B and C viral infection and its influence on progression of ALD and hepatocellular carcinoma (HCC).
3. The pattern of AFP and GGT alteration in ALD.
4. The value of CAGE questionnaire in diagnosis of ALD.
5. The value of left-to-right PV ratio in sonographic diagnosis of ALD.

6. Determine the outcome of patients with DF > 32 and compare those treated with corticosteroids with those with conventional treatment.

Statistical analysis: Chi square tests and Fishers exact tests were used for comparison of the groups with each other.

Results:

Of the 113 alcoholic patients attending the gastroenterology and hepatolgy teaching hospital between December 2001 and December 2003. The most common presenting symptom was jaundice (62.8%), anorexia, weight loss (39.8-54%) followed by hematemesis and malena (46.9%) and encephalopathy (41%). The pattern of the bowel motion was predominantly diarrhea (40.7%), constipation (17%). Fever in the absence of demonstrable infection in (16.8%) as shown in table 1.

Table 1: Symptoms of ALD

	Group 1 (n=43) Mild		Group 2 (n=26) Moderate		Group 3 (n=44) Severe		Overall (n=113)	
Symptoms	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Hematemesis and Malena	16	37.2	12	46.2	25	56.8	53	46.9
Anorexia	20	46.5	15	57.7	26	59.1	61	54.0
Weight loss	17	39.5	8	30.8	12	27.3	45	39.8
Fever	6	14.0	6	23.1	7	15.9	19	16.8
Encephalopathy	5	11.6	10	38.5	27	61.4	46	40.7
Diarrhea	17	39.5	11	42.3	27	61.4	54	47.8
Constipation	9	20.9	3	11.5	10	22.7	19	16.8

Moderate disease was defined by bilirubin level >5mg/dl and severe disease by bilirubin level >5mg/dl and PT>4 seconds prolonged [(16)].

The most common physical finding was hepatomegaly in (71%) followed by jaundice and ascites in (63%). The most common EGD finding was esophageal varieses in (77%), PHT gastropathy (52%), hemorrhagic gastritis (10.6%), GERD, lax cardia (9-15%) and esophageal candidiasis (4.4%). Macrocytic anemia was found in (70%) with a mean of mean corpuscular volume (MCV) 103.6 fl. Leucocytosis was common with a mean white blood count (WBC) of 11600 cells/mm^3. The serum aminotransferase was mildly elevated and the AST/ALT ratio often exceed 2.The serum bilirubin and PT positively correlated with the severity of ALD.There was a negative correlation between serum albumin the severity of ALD. The serum alkaline phosphatase (ALP) was moderately elevated (2-3 times) and the level of GGT was commonly elevated in alcoholics irrespective of liver damage. AFP was bellow normal in 80% and was negatively correlated with the severity of ALD. Triglyceride (TG) was mildly elevated while serum cholesterol was normal. The serum ferritin exceed 332 microgram/L in 60%as in table(2)

Table (2): Laboratory values in ALD

	GROUP 1 (n 43) Mild	GROUP 2 (n 26) Moderate	GROUP 3 (n 44) Severe
Hematocrit (%)	38.6	34	33
MCV (mic/mm^3	100	104	107
WBC (per mm^3)	8700	9300	11600
AST U/L	62	89	66
ALT U/L	50	59	54
ALP (IU/Ml)	145	165	155
S. Bilirubin(mg/dl)	2.3	12.8	4.8
PT sec. Prolong	2.3	3.8	9.3
S. Albumin gm/dl	3.2	3.8	2.15
AFP ng/ml	8.4	7.1	5.2
GGT u/l	62.3	75	58
S. Cholesterol	162	169	175
S. TG mg/dl	134	147	177
HDL mg/dl	44	30	28
S.ferritin mic/l	457	417	326

The prevalence of hepatitis B virus (HBV) infection was (17.7%) and hepatitis C virus (HCV) was (11.5%) table (3).

Table (3): The prevalence of viral hepatitis in ALD patient

	Overall (n=113)	
	N	**%**
Viral Hepatitis B	20	17.7
Viral Hepatitis C	13	11.5
Total	33	29.2

The prevalence of (HCC) showed a statistically significant positive trend with severity of ALD, it increased from 4.7% among those with mild ALD to as high as 18.2% in those with severe disease, their mean age was 58 years and the mean of AFP was 15.5 ng/ml as in table (4).

Table (4): The prevalence of HCC according to the severity of ALD

		HCC	
Severity of ADL	**Total**	**N**	**%**
Mild	43	2	4.7
Moderate	26	2	7.7
Severe	44	8	18.2
Overall	113	12	10.6

P (trend) = 0.04

The risk of having HCC among those with positive viral marker is 9.6 times that of those with negative marker. The prevalence rate of positive viral marker among those with HCC (75%) was significantly higher than that of those with no HCC (23.8%) as in table (5).

Table (5): The prevalence of HCC related to hepatitis virus

	HCC					
	Present		**Absent**		**Total**	
	N	**%**	**N**	**%**	**N**	**%**
Viral markers						
Positive	9	75	24	23.8	33	29.2
Negative	3	25	77	76.2	80	70.8
Total	12	100	101	100	113	100
OR=9.6 (2.1-58.2)						
P < 0.001						

In CAGE questionnaire, the majority (85%) scores 2 and more as in table (6).

Table (6): CAGE Questionnaire Score in ALD

Score > 2	85%
Score < 2	15%

The LT-RT PV ratio measured in 50 patients with ALD and compared to 50 age matched control AND 50 patients with CLD (not alcoholic), there was significant correlation between LT-TR PV ratio = or > 1 and ALD. Table (7)

Table (7): LT-RT PV ratio > 1 in ALD and control

LT-RT PV ratio	ALD	Healthy c	P value (1)	CLD	P value (2)
+ve (>=1)	**42**	**5**	**<0.001**	**32**	**<0.025**
-ve (<1)	**8**	**45**		**18**	
Total	**50**	**50**		**50**	

P (1) (χ^2)< 0.001. Sensitivity = 84%Specificity = 90%PPV = 89.4%NPV = 84.9%
False +ve = 10%False -ve = 16%Accuracy = 87% p (2) <0.025 (sig.).

Table (8) showed that there was significant improvement in survival in ALD patient treated with prednisolone. The survival rate at one year was 90% in prednisolone group and 29% in those who received conventional treatment.

Table (8) Prednisolone therapy compared to those with conventional treatment, incidence of death after one year of follow up

	N	%
Prednisolone therapy (n=10)	1	10
Conventional therapy (n=21)	15	71.4

P (Fisher's exact test) = 0.002

RR of survival with prdnisolone therapy compared to conventional treat. = 7.1

Discussion:

In this study the most the most common clinical manifestation of ALD was jaundice (63%) and hepatomegaly (71%). Liver enlargement can be detected in more than 75% of patients who are actively drinking and observed consistently at all stages of liver injury. Hepatomegaly is related in part to the accumulation of fat within liver cells. Hepatocyte swelling, rather than steatosis, is believed to the major cause of liver enlargement in moderately to severe ALD. The frequency of jaundice increased as the disease progresses. Unusually large proportion exhibits hepatic encephalopathy (41%) even in-patients with mild disease (12%). Chedid and colleagues have confirmed this finding. [17] The pattern of the bowel was predominantly diarrhea (40%). Diarrhea with steatorrhea can be related to decreased biliary excretion of bile salts, pancreatic insufficiency and to a direct, toxic effect of alcohol on the intestinal mucosa, reversible intestinal abnormalities in alcoholics include malabsorption of folic acid, thiamine, nitrogen, B12 and B2.Decreased output of HCO3, amylase thiamin, and chemotrypsin in response to secretin. [18] The serum aminotransferase is only modestly elevated and does not correlate with disease severity [19], the most common pattern in ALD is disproportionate elevation of AST compared to ALT, the ratio is usually greater than 2 and have been attributed to pyridoxine deficiency, which is a co-factor for the activity of ALT. According to this hypothesis the altered ratio reflect a failure of appropriate increase in the ALT rather than a disproportionate elevation in AST [20]. The GGT is usually elevated in heavy drinkers, irrespective of the presence of liver disease and is widely used as screening test for alcoholic abuse. The rise results mainly from enzyme induction, although hepatocellular damage and cholestasis may contribute and the level may return to normal within few weeks of abstinence, its 72% sensitive and 80% specific for the diagnosis of ALD. [21] The AFP value was bellow normal in 80%. This result is in consistence with Mendenhall who found value bellow normal in 78% and 42% had undetectable level, clinically lowest AFP was observed in the more severely ill patients. Correlation analysis showed a significant relationship of AFP to visceral protein concentration, (i.e., albumin, and transferrin). These finding suggest that AFP is a good index of disease prognosis [22] The prevalence of HBV in this study was 18% and HCV 11%. Renard founded that the prevalence of HBV was 26.9 %.[23] Mendenhall concluded that 18.4% of ALD reacted serologically for HCV [24]. Alcohol accelerates fibrosis progression and increases the risk of cirrhosis and HCC and decreases the efficacy of interferon therapy [25]. HCC prevalence in ALD is increased in our study and is positively correlated with the severity of ALD and is significantly correlated with hepatitis viral infection.

HCC is among the 10 most common tumors in the world. Chronic HBV is probably the most common cause, followed by chronic HCV; other important cause is ALD [55]. Ohhira concluded that in 180 HCC patients who were admitted to Asahikawa medical college hospital, 6% had HCC associated with pure ALD, whereas 86.6% was associated with chronic viral hepatitis [27]. In CAGE questionnaire the majority (82%) of patients in our study score 2 and more. The predictive value of the CAGE criteria depends upon the prevalence of alcoholism in the population to which it applied. A positive response to at least 2 questions is seen in the majority of patients with alcoholism and to all four questions in approximately 55% [28, 29]. Girela found that CAGE questionnaire was the most efficient (96% sensitive and 92% specific) in the diagnosis of alcoholism [30]. The LT-RT PV ratio equal to or >1 was significantly correlated with ALD that is consistent with Trigaux result. [31] There are no characteristic radiological features of ALD; the most common finding is hepatic steatosis, detectable by increased echogenicity on sonography. It emerge from Trigaux and our study that LT PV > or equal to RT PV represent a useful ultrasonographic sign of ALD, corresponding to a relative enlargement of the left hepatic lobe compared with the right [31]. In this study DF >32 was found in 31 patients who were divided into two groups the first one (10 patients) received prednisolone 40 mg for one month and tapered over one month and the second group (21 patients) received conventional treatment and both followed for a year. In the treated group encephalopathy was present in 86% and the mean WBC was 11500/c.mm. Prednisolone therapy was associated with significant improvement in survival rate at one year. Between 1971 and 1989, at least 12 published placebo controlled trials examined the effect of glucocorticoids on patients who had acute ALD.

Cumulative results of 12 clinical trials and our study (bolt) in which therapy with Prednisolone was compared with placebo therapy.

Prednisolone			***Conventional treatment***			
Died	**Total**	**%**	**Died**	**Total**	**%**	**P**
1	20	5.0	6	17	35.3	< 0.01
6	11	54.5	7	9	77.8	Ns
7	20	35.0	9	25	36.0	Ns
6	12	50.0	5	16	34.3	Ns
2	7	28.62	2	7	28.6	< 0.01
6	12	50	7	15	46.7	Ns
1	24	4.2	6	31	19.4	Ns
7	15	53.3	7	13	53.8	Ns
17	27	63.0	16	28	57.1	Ns
22	94	23.4	25	93	26.9	NS
2	35	5.7	11	31	35.5	0.006
4	32	12.5	16	29	55.2	0.001
1	**10**	**10**	**15**	**21**	**71**	**0.001**

Only 4 of the 12 trials and our trial demonstrated a reduction in short-term mortality by glucocorticoids. . Imperiale and McCullough performed a meta-analysis of 11 clinical trials. Encephalopathy was the strongest predictor of a response to glucocorticoids. Of note, the study by Mathurin and colleagues was the first to report long-term follow-up data for patients treated with glucocorticoids for alcoholic hepatitis. Their results indicated that the survival benefit of a 4-week course of prednisolone lasted for at least 1 year [(32)] that is consistent with our results. Glucocorticoids are considered sufficiently beneficial to be recommended for treatment of alcoholic hepatitis [(33)].

In conclusion:

In Iraqi patients with ALD, the most common clinical manifestations were jaundice and hepatomegaly. The GGT was commonly elevated irrespective of liver damage. AFP was bellow normal in the majority and is negatively correlated with the severity of ALD. The HBV and HCV were fairly prevalent and were significantly correlated with the severity of ALD and HCC.The CAGE questionnaire was sensitive in the diagnosis of ALD. The LT-RT PV ratio equal to one or more was valid in sonographgic diagnosis of ALD. Glucocorticoid was effective in reducing mortality at one year in patients with DF>32.

References:

1. Pequignot GB, Cyrulink F: Chronic disease due to overconssumption of alcoholic drink. In International Encyclopaedia of Pharmacology and Therapeutics, vol.2. Pergamon Press, Oxford, 1970,pp. 375-412.
2. Bosron WF, Ehng T. Li TK: Genetic factors in alcohol metabolism and alcoholism. Semin Liver Dis 13:126, 1993.
3. Frezza M: High blood alcohol level in women: The role of decreased gastric alcohol dehydrogenase activity and first pass metabolism. N Engl J Med 322:95, 1990.
4. Mendenhall CL: Relevance of anti-HCV reactivity in patients with alcoholic hepatitis. Gastroenterol Jpn 28:15, 1993.
5. Mendenhall CL: Protein-calorie malnutrition associated with alcoholic hepatitis. Am J Med 76:211, 1984.
6. Naveau, S, Giraud, V, Borotto, E, et al: Excess Weight risk factor for alcoholic liver disease. Hepatology 25:108, 1997.
7. Thuluvath, P, Wojno, KJ, Yardley, JH, Mezey, E: Effects of helicobacter pylori infection and gastritis on gastric alcohol dehydrogenase activity. Alcohol Clin Exp Res 18:795, 1994.
8. Klatsky AL, Armstrong MA: Alcohol, smoking, coffee, and cirrhosis. Am J Epidemiol 322:95, 1992.
9. Stal, P, Hultcrantz, R: Iron increases ethanol toxicity in rat liver. J Hepatol 17:108,1992.
10. Ji, S, Lemaster, JJ, Chrestenson, V, Thurman, RG: Periportal and pericentrl hypoxia pyridine nuceotide fluorescence from the surface of the perfused liver : Evaluation of the hypothesis that chronic treatment with ethanol produces pericentral hypoxia. Proc Natl Acad Sci U S A 79:5415, 1982.
11. Sheron, N, Bird, G, Koskinas, J, et al: Circulating and tissue level of the neutrophil chemotaxin interleukin-8 are elevated in severe acute alcoholic hepatitis, and tissue levels correlate with neutrophil infiltration. Hepatology 1993; 18:41.
12. Nanji, AA, Miao, L, Thomas, P, et al: Enhanced cyclooxygenase-2 gene expression in alcoholic liver disease in the rat. Gasreoenterology 1997; 112:943.
13. Niemela, O, Parkilla, S, Yla-Herttuala, S, et al: Covalent protein adduct in the liver as a result of ethanol metabolism and lipid peroxidation. Lab Inves 1994; 70:537.

14. Achord JL: Malnutrition and the role of nutritional support in alcoholic liver disease. Am J Gastroenterol 82:1, 1987.
15. Orrego H, Blake, Blendis LM, et al: Assessment of prognostic factors in alcoholic liver disease. Hepatology 3:896, 1983.
16. Mendenhall CL: Alcoholic hepatitis. Clin Gastroenerol 10:420, 1981.
17. Morgan MY, Sherlock S, Scheuer PJ: Acute cholestasis, hepatic failure and fatty liver in alcoholic. Scand. J. Gastroenterol 13:299; 1978.
18. Mezey E: Intestinal function in chronic alcoholism. Ann NY Acad Sci 252:215, 1975.
19. Mihas C, Tavassoli M: Laboratory markers of ethabnol intake and abuse. Am J Med Sci 303:415, 1992.
20. Diehl AM, Potter J, Boitnot J, et al: Relationship between pyridoxal 5-phosphate deficiency and aminotransferase level in alcoholic hepatitis. Gastroenterology 86:632, 1984.
21. Bellini M, Tumino E, Giordani R, et al: Serum gamma-glutamyl-transpeptidase isoform in alcoholic liver disease. Alcohol-Alcohol 32(3): 259-66, 1997.
22. Mandenhall CL, Chedid A, French SW, et al: Alpha-fetoprotien alteratin in alcoholics with liver disease. Alcohol-Alcohol 26(5-6): 527-
23. .Renard P, Hillon P, Bedenne L, et al: Markers of hepatitis B virus and chronic alcoholism. Ann-Gastroenterlo-Hepatol -Paris 27(1): 7-12, 1991.
24. Mendenhall CL, Mortiz T, Rouster S, et al: Epidemiology of hepatitis C among veterans with alcoholic liver disease. Am-J-Gastroenterol88(7):1022-6, 1993.
25. Marsona LS, Pena LR: The interaction of alcoholic liver disease and hepatitis C. Hepatogastroenterology 45(20): 331-9, 1998.
26. Sherman M: Hepatocellular carcinoma. Gastroenterologist 3(1): 55-66, 1995.
27. Ohhira M, Fujimoto Y, Matsumoto A, et al: Hepatocellular carcinoma associated with alcoholic liver disease. Alcohol -Cini-Exp-Res 20(9): 378-382, 1996.
28. Ewing JA: Detecting alcoholism: The CAGE questionnaire. JAMA 115: 774, 1905.
29. Buchsbaum D, Buchanan RG, Centor RM, et al: Screening for alcohol abuse using CAGE scores and likelihood ratio. Ann Intern Med 115: 774, 1991.
30. Girela E, Villanueva E, Luna JD, et al: Comparison of the CAGE questionnaire versus some biochemical markers in the diagnosis of alcoholism. Alcohol-Alcohol 92(3): 337-43, 1994.
31. Trigaux JP, Melange M, Buysschaert M, et al: Alcoholic liver disease: value of the left-to-right portal vein in its sonographic diagnosis. Gastrointest-radiol 16:215-23, 1991.
32. Mendenhall CL, et al: Short term and long term survival in patients with alcoholic hepatitis treated with oxandrolone and prednisolone. N Engl J Med 311:1464, 1984.
33. McCullough AJ, O Connor JF: Alcoholic liver disease: Proposed recommendation for the American College of Gastroenterlogy. Am J Gastroenterol 93:2022, 1998.