

MIOCARDIUM/ENDOCARDIUM/PERICARDIUM

Infective Endocarditis in Patients With Chronic Liver Disease: Clinical and Prognostic Assessment

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Introduction and objectives. Chronic liver disease increases the susceptibility to bacterial infections and infective endocarditis. Our aim was to determine the clinical and microbiological features and the prognosis in patients with chronic liver disease who also had infective endocarditis.

Patients and method. One hundred and seventy-four consecutive inpatients at our institution were recruited and followed. Thirty of them had chronic liver disease. Clinical, microbiological and echocardiographic variables were analyzed and, in some cases, histological variables were also recorded.

Results. Patients with chronic liver disease were younger (36 ± 11 vs 54 ± 18 years; $p < 0.01$) and had a larger proportion of intravenous drug users (73 vs 16%; $p < 0.01$), HIV infection (47 vs 10%; $p < 0.01$), right valve involvement and spleen enlargement, but heart failure appeared less often (7 vs 34%; $p = 0.003$). Thirty percent of the patients with and 51% of patients without chronic liver disease underwent surgery for infective endocarditis. Total mortality among patients with and without chronic liver disease was 40% and 31%, respectively. After adjustment for age and for the incidence of congestive heart failure, chronic liver disease doubled mid-term mortality with a RR = 2.45 ($p = 0.015$).

Conclusions. Chronic liver disease has a significant impact on the prognosis in patients with infective endocarditis, and these patients should therefore be considered a high risk group.

Key words: *Surgery. Complications. Endocardium. Endocarditis. Follow-up studies.*

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Endocarditis infecciosa en pacientes con hepatopatía crónica: valoración clínica y pronóstica

Introducción y objetivos. La enfermedad hepática crónica produce un aumento de la susceptibilidad a padecer infecciones bacterianas y, específicamente, endocarditis infecciosa. Nuestro objetivo fue evaluar el espectro microbiológico, las peculiaridades clínicas y el pronóstico de los pacientes hepatópatas con endocarditis infecciosa.

Pacientes y método. Un total de 174 pacientes consecutivos ingresados en nuestro hospital con el diagnóstico de endocarditis infecciosa fueron evaluados y seguidos. De ellos, 30 habían sido diagnosticados previamente de hepatopatía crónica.

Resultados. Los pacientes con hepatopatía crónica fueron más jóvenes (36 ± 11 frente a 54 ± 18 años; $p < 0,01$), presentaron mayor frecuencia de uso de drogas por vía parenteral (73 frente a 16%; $p < 0,01$), infección por el VIH (47 frente a 10%; $p < 0,01$), afección de las válvulas derechas, esplenomegalia e infección por *Staphylococcus aureus*, mientras que era más raro el desarrollo de insuficiencia cardíaca (7 frente a 34%; $p = 0,003$). Fueron intervenidos el 30% de los pacientes con una hepatopatía y el 51% de los que no la presentaban. El 40% de los pacientes hepatópatas y el 31% de los no hepatópatas fallecieron durante el seguimiento. Una vez ajustado por la edad y el desarrollo de insuficiencia cardíaca, se observó que la presencia de hepatopatía incrementaba de forma independiente en aproximadamente dos veces y media la mortalidad (RR = 2,45; $p = 0,015$).

Conclusiones. La endocarditis infecciosa presenta una serie de características diferenciales en pacientes con hepatopatía crónica. La presencia de hepatopatía crónica condiciona un empeoramiento del pronóstico vital, por lo que estos pacientes deben ser considerados de alto riesgo.

Palabras clave: *Cirugía. Complicaciones. Endocardio. Endocarditis. Estudios de seguimiento.*

ABBREVIATIONS

IE: infective endocarditis.
HIV: human immunodeficiency virus.

INTRODUCTION

Chronic liver disease increases the susceptibility to bacterial infections.¹ In particular, infective endocarditis (IE) is more common in patients with chronic liver disease than in those without liver disease.^{2,3} Unless IE is strongly suspected, diagnosis is difficult because the signs and symptoms may be confused by systemic deterioration due to liver disease.

We decided to perform this study because this group of patients is not well represented in the scientific literature. Only small, relatively inhomogeneous patient populations can be found, and results vary from one study to the next.^{4,5} The clinical characteristics or the clinical course of patients with chronic liver disease and IE are thus not well defined. Identifying possible prognostic factors in these patients is difficult because of the coexistence of the two diseases. For example, we do not know whether hepatic damage prior to the development of endocarditis can influence the prognosis of these patients or whether such damage can alter the clinical course of IE.

The objective of the present work was to compare the special clinical features and the microbiological spectrum of patients with and without chronic liver disease, and to investigate whether chronic liver disease affects the short- and long-term prognosis of endocarditis.

PATIENTS AND METHODS

Study population

This study was conducted in our hospital, which is a tertiary care center that serves a population of more than 500 000 people, and is the reference hospital for diagnostic tests of heart disease and heart surgery. We retrospectively evaluated 174 consecutive patients admitted to our hospital with IE by reviewing their hospital record, and then followed them prospectively. All patients were diagnosed with IE as defined by the Durack criteria.⁶ We only enrolled patients with definite diagnosis of IE, established through isolation of the infective agent or

histology with specific endocardial vegetation or embolic material (in the operating theater or a post mortem study), or a high probability of IE according to clinical, microbiological and echocardiographic data interpreted in accordance with the aforementioned criteria.

Echocardiographic study

In our hospital all patients with suspected IE undergo transthoracic echocardiography and, if appropriate, transesophageal echocardiography, regardless of the results of blood cultures. All studies were performed by staff with experience in the echocardiography laboratory. A two-dimensional M-mode echocardiogram and a pulsed- and continuous-wave Doppler color study were systematically performed on all patients. Before transesophageal echocardiography, patients were asked to give informed consent to perform the procedure. A lidocaine aerosol was administered to anesthetize the oropharynx and midazolam 1 mg and meperidine 12.5 mg were injected intravenously before the probe was introduced.

Study outcomes and definitions

We created a database to collect baseline characteristics and follow-up data. Clinical variables were recorded such as age, sex, pathological history of interest, human immunodeficiency virus (HIV) status, and fever (defined as temperature greater than 38 °C) and leukocytosis (defined as a mean leukocyte count greater than 10.5×10^3 leukocytes per deciliter). Microbiological variables were also recorded, such as the germ causing endocarditis, presence of polymicrobial infection, presence of negative blood cultures (defined as at least two different negative cultures at the time of discharge from hospital), and cardiac and extracardiac risk factors for development of IE, such as valve disorders of different origins or a heart valve prosthesis. In addition, we collected data on the progression of endocarditis, such as the appearance of anatomical complications of endocarditis, the appearance of vascular disorders (including petechiae, splinter hemorrhages, Janeway lesions or Osler nodes) or the appearance of life events. The Results section and corresponding tables present the outcomes studied in detail.

Diagnosis of chronic liver disease

Chronic liver disease was defined as an inflammatory disease of the liver lasting more than 6 months, manifested as an increase in transaminases and histologically through inflammation of the

portohepatic space. The definition also included liver pathologies resulting from the progression of this process, particularly liver cirrhosis. The etiological diagnosis of liver disease was performed by clinical history, serology for hepatotropic viruses and/or liver histology. Histological alterations such as diffuse liver disease and the presence of fibrosis and regenerating nodules were used to define whether the patient had liver cirrhosis. The diagnosis of chronic liver disease was performed by the digestive system service of our hospital.

Follow-up

The follow-up of the patients was performed by regular visits to the cardiology service, analysis of clinical documentation, telephone calls and clinical visits. The primary outcome measure of the study was death of the patient due to IE progression, complications derived from IE or the therapeutic methods used to treat IE.

Statistical analysis

We used the SPSS 9.0 statistical package to analyze the data. The quantitative outcomes were described as mean±standard deviation. Categorical outcomes were described as the absolute value followed by the percentage. For quantitative outcomes, we analyzed differences between the two patient groups with Student's *t* test. Differences in categorical outcomes were assessed with the χ^2 test or Fisher's test. A *P* value of <.05 was considered statistically significant. Survival data were presented as a Kaplan-Meier plot. The last contact with the patient or when the patient died due to causes not directly related to IE was taken as the censor time. Comparison of the survival curves for patients with and without liver disease was performed with the log-rank test. The survival data were then analyzed with the Cox proportional hazards analysis to identify the factors predictive of mortality in the different patient groups. A univariate analysis was performed first before proceeding with multivariate analysis. The multivariate analysis included the variables that had been predictive of survival in the univariate analysis, along with the presence of liver disease and variables that could theoretically influence the prognosis of these patients, using forward inclusion sequences with input and output significance criteria of *P*<0.05 and *P*<0.1, respectively.

RESULTS

For the patients with liver disease, chronic viral hepatitis B was diagnosed in three patients (10%),

hepatitis C in eight patients (27%), both hepatitis B and C in nine patients (30%), alcoholic hepatitis in one patient (3%), and no cause of liver disease could be determined in nine patients (30%). Liver cirrhosis was not diagnosed in any patient. Table 1 shows the baseline characteristics of these patients. Analysis of the overall subject population (n=174) shows that patients with chronic liver disease (n=30; 17%) were significantly younger than those without chronic liver disease (36±11 years versus 54±18 years; *P*<.01). The distribution by sex was similar, with twice as many men as women in both groups. More patients with liver disease had HIV infection (47% vs 10%; *P*<.01) and splenomegaly was also more common (40% vs 9%; *P*<.01) in these patients. During the study, the development of heart failure due to IE before or during the first admission to our hospital was less frequent than in patients without liver disease. The appearance of fever, presence of vascular disorders or leukocytosis did not differ between the two patient groups. When we analyzed the site of infection (Table 1), we found a significant difference only for infection of the tricuspid valve, this condition being more

TABLE 1. Baseline characteristics

	With chronic liver disease	Without chronic liver disease	<i>P</i>
	30 (17%)	144 (83%)	
Age, years	36±11	54±18	<.01
Sex			
Women	10 (33%)	49 (34%)	NS
Men	20 (67%)	95 (66%)	
HIV infection	14 (47%)	15 (10%)	<.01
Fever	25 (83%)	108 (75%)	NS
CHF before or during hospitalization	4 (13%)	45 (32%)	.045
Splenomegaly	12 (40%)	13 (9%)	<.01
Vascular phenomena	4 (13%)	13 (9%)	NS
Leukocytosis	16 (55%)	66 (46%)	NS
Risk factors			
IVDU	22 (73%)	23 (16%)	<.01
Previous IE	5 (17%)	10 (7%)	NS
Valve prosthesis	7 (23%)	46 (32%)	NS
PPM	0	9 (6%)	NS
Degenerative valve disease	1 (3%)	27 (19%)	.052
Rheumatic valve disease	5 (17%)	29 (20%)	NS
Congenital valve disease	4 (13%)	17 (12%)	NS
Site			
Mitral valve	5 (10%)	46 (32%)	NS
Aortic valve	6 (20%)	45 (31%)	NS
Tricuspid valve	13 (43%)	16 (11%)	<.01
Pulmonary valve	1 (3%)	2 (1%)	NS
Mitral prosthesis	5 (17%)	27 (19%)	NS
Aortic prosthesis	2 (7%)	21 (15%)	NS
PPM	0	9 (6%)	NS
Multiple valve IE	2 (7%)	22 (15%)	NS

IVDU indicates intravenous drug users; IE, infective endocarditis; CHF, congestive heart failure; PPM, permanent pacemaker.

frequent in patients with liver disease.

Examination of the risk factors for developing IE shows the following: the only significant differences were a larger proportion of intravenous drug users among those who had chronic liver disease and, among this subpopulation, a smaller proportion of degenerative valve disorders, although this latter finding was only just significant. No significant differences were found for the history of IE before the episode that led to enrollment of the patient in the study, heart valve prosthesis or a permanent pacemaker, or any other type of valve disorder.

The microbiological spectrum of IE is presented in Table 2. In more than 76% of patients from both groups, microbiological diagnosis of the germ causing IE was obtained from a blood culture. *Staphylococcus aureus* was the most common bacterium causing IE in patients with liver disease. Other less common microorganisms causing endocarditis in patients with chronic liver disease were *S. epidermidis* and *S. viridans*. However, no significant differences were obtained in the statistical analysis.

The patients were studied and followed for a mean of 25.4±41.5 months. Table 3 summarizes the study outcomes. There were no statistically significant differences in the development of anatomical complications (perivalvular abscesses, free wall rupture to the pericardium, shunts, pseudoaneurysms or mycotic aneurysms) between the two groups of patient. Likewise, no differences were observed in the need for surgery during hospitalization or in hospital mortality. For progression of IE, patients with chronic liver disease had a higher number of pulmonary or systemic embolic events, although this difference did not reach statistical significance (53% vs 35%; $P=.07$). Specifically, four of the patients with chronic liver disease had systemic arterial embolisms (13% of patients with liver disease and 25% of total embolisms) and 12 had pulmonary embolisms (40% of patients with liver disease and 75% of total embolisms). However, a statistically significant tendency to develop heart failure less often was observed in patients with liver disease ($P=.003$)

The curves obtained in Figure 1 were obtained after

TABLE 2. Microbiological characteristics

	With chronic liver disease	Without chronic liver disease	P
Positive blood cultures	23 (77%)	109 (76%)	NS
Multiple IE	1 (4%)*	9 (8%)*	NS
<i>S. aureus</i>	14 (61%)*	39 (36%)*	
<i>S. epidermidis</i>	4 (17%)*	18 (17%)*	
<i>S. viridans</i>	2 (9%)*	18 (17%)*	
Others	2 (9%)	25 (23%)	

*Percentage with respect to total number of patients with positive blood cultures in each group. IE indicates infective endocarditis.

survival analysis of the data with the Kaplan-Meier method. The median survival of patients without chronic liver disease was 73±9.53 months, while for patients with chronic liver disease it was 38±11.23 months. The causes of mortality in patients with liver disease were: heart failure in two patients (7% of patients with liver disease; 17% of deaths in patients with liver disease), arterial embolism in one patient (3% of patients with liver disease; 8% of deaths in patients with liver disease), sepsis in eight patients (27% of patients with liver disease; 67% of deaths in patients with liver disease) and postoperative complications after a cardiovascular intervention in one case (3% of patients with liver disease; 8% of deaths in patients with liver disease). When the two survival curves were compared with the log-rank test, no statistically significant differences were found ($P=.3035$). There was no statistically significant difference either when a univariate analysis was performed with the Cox model (Table 4). Significant differences were found although for a bivariate analysis with age and presence of liver disease and for a multivariate analysis with variables from the univariate analysis that were significant at the $P<.1$ level. These multivariate variables were development of heart failure, prosthetic endocarditis and age, along with other variables that, although they did not reach statistical significance, could theoretically modify the survival results, namely, HIV infection and intravenous drug use. According to the adjusted model, the presence of chronic liver disease increased the risk of mortality in patients with IE by approximately two and a half times compared to patients without liver disease.

DISCUSSION

The liver plays an important part in the defense against bacterial infections,¹⁻³ and liver disease can increase susceptibility to infection. In particular,

TABLE 3. Follow-up

	With chronic liver disease	Without chronic liver disease	P
Anatomical complications	8 (28%)	52 (36%)	NS
Development of CHF	2 (7%)	49 (34%)	.003
Embolisms	16 (53%)	51 (35%)	.07
Hospital surgery	8 (27%)	66 (46%)	.05
Hospital death	6 (20%)	24 (17%)	NS
Surgery (total during follow-up)	9 (30%)	74 (51%)	NS
Death secondary to infective endocarditis (total during follow-up)	12 (40%)	43 (31%)	NS
Total	53	293	NS

CHF indicates congestive heart failure.

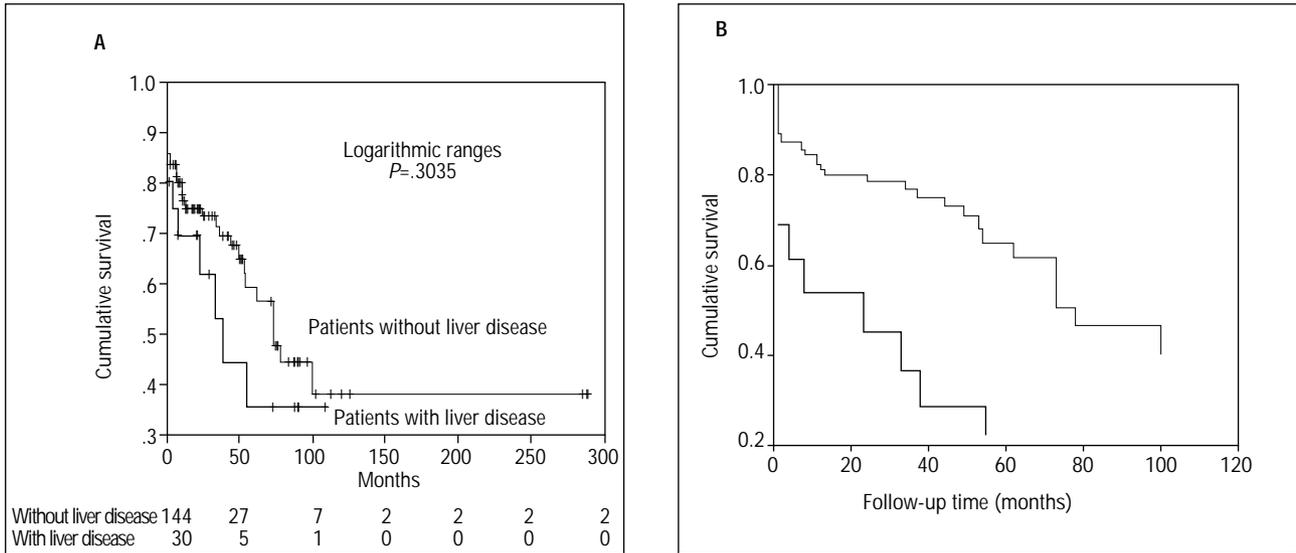


Fig. 1. A: Descriptive cumulative survival curves for mortality in patients with liver disease versus patients without liver disease. The months of follow-up are indicated on the abscissa and below each month the number of patients at risk at each time is shown. B: Cumulative survival curves in patients with and without liver disease, adjusted for age and development of heart disease.

chronic liver disease has been associated with an increase in the susceptibility to IE.³ There are many different causes, for example, dysfunction of the mucosa barrier, relative deficiency of immunoglobulins and complement components and dysfunction of the reticuloendothelial system.⁷ Blood stasis and shunting through perihepatic collateral veins occur with cirrhosis and portal hypertension,⁸ encouraging the persistence of the bacteremia⁹ and increasing vulnerability to endocarditis.

Earlier articles have described the characteristics and prognostic implications for a variety of subpopulations of patients affected by IE, such as diabetic patients¹⁰ or older patients,¹¹ but there are few studies that relate endocarditis with chronic liver disease. The only results available are for reduced

populations with a large variety of patients that give contradictory results. McCashland et al,⁴ with a population of 8 patients, found that IE in patients with liver disease was more common in women, characteristically affecting the mitral valve and that the microorganism most commonly implicated was *S. aureus*. According to Otones et al,³ who analyzed 16 patients, the most common germ that caused endocarditis was *Enterococcus* in patients with urinary and gastrointestinal infections, and *Streptococcus* in a second group of patients with alcoholic liver disease, although the origin of the infection was not known in 61% of the patients. The main site of infection was the aortic valve and the distribution by sexes was similar between men and women. There were no significant differences in the appearance of culture-negative IE between the two patient groups. The influence of this variable on prognosis has been studied in other publications.¹²⁻¹³

In contrast, our patient population was large and the follow-up period was long, making our study the first of its kind published in the scientific literature. On analyzing our results, we find certain particular features of IE in patients with prior chronic liver disease that may derive from the characteristics of the patients included. We found a greater prevalence of staphylococcal infection and tricuspid involvement, possibly because of the large number of intravenous drug users enrolled, in contrast to other studies where mitral or aortic affliction were more common. Another interesting point that differentiates our study from the populations published previously is that, in recent years, the increase in intravenous drug use has not only changed the presentation of endocarditis but also the cause of chronic liver diseases. Our population is

TABLE 4. Analysis of survival with the Cox method*

Model	Variable	Risk ratio	95% CI	P
1	CLD	1.38	0.73-2.62	.33
	Age	1.023	1.008-1.0385	0.0023
	CHF	2.2	1.26-3.84	0.005
	HIV	1.04	0.53-2	NS
	IVDU	0.76	0.4-1.44	NS
	Prosthetic IE	1.76	1.024-3.028	.041
2	CLD	2.59	1.22-5.45	.012
	Age	1.03	1.015-1.05	0.0003
3	CLD	2.32	1.12-4.83	.024
	Age	1.024	1.005-1.044	0.012
	CHF	1.97	1.12-3.47	0.019

*Model 1 shows the univariate analysis, model 2 the bivariate analysis and model 3 the final multivariate analysis. IE indicates infective endocarditis; CLD, chronic liver disease; 95% CI, 95% confidence interval of the risk ratio; CHF, development of congestive heart failure.

more representative of current patients.

Patients with liver disease develop heart failure less often, probably because they are younger and have a greater proportion of right-valve involvement. The presence of a greater proportion of patients with splenomegaly among the patients with liver disease can be explained by the endocarditis itself, by advanced liver disease, or by progression to disease (AIDS) in HIV positive patients.

The lower need for intrahospital surgery ($P=.05$) might be because of the lower appearance of heart failure in a group of patients that is younger, with less prior degenerative valve disorder and with right valves, particularly the tricuspid valve, affected more often. On the contrary, assessment of hospital surgery in endocarditis depends on the degree of hepatic dysfunction, as severe hepatic impairment (serious alterations in coagulation, metabolic dysfunction, etc.) is associated with a very high mortality during the perioperative period. An exhaustive assessment of comorbidity is therefore necessary before surgery.

The common coexistence of intravenous drug use and HIV infection with liver disease might suggest that differences in prognosis depend more on intravenous drug use or HIV infection than on the liver disease itself. According to the results from previous studies, HIV infection does not seem to influence the incidence, clinical manifestations, bacteriology or prognosis of IE.^{14,15} On the other hand, IE in intravenous drug users generally has a favorable prognosis when it affects right valves, but not when the aortic valve is affected. In agreement with these data, these variables did not significantly change the prognosis of patients in our study when we analyzed the influence of chronic liver disease on life expectancy. Although right endocarditis usually has a more favorable prognosis, which should improve survival results in patients with liver disease compared to those without, patients with liver disease have worse survival results.

Despite the greater incidence of bacteremia in this type of patient,^{5,16,17} diagnosis of IE is uncommon. Infective endocarditis can be manifested through the presence of fever, a general deterioration or an increase in encephalopathy or nephropathy, and so may escape unnoticed unless clinical suspicion is strong. Extensive gastrointestinal bleeding seems to be the most common cause of bacteremia,¹⁷ although the significant diagnostic and therapeutic procedures the patients go through, such as venous catheterization, liver biopsies or genitourinary examinations, may cause infection. The recommendation of antibiotic prophylaxis in this type of patient is doubtful. Moreover, the prognosis is not the only factor to be affected in these patients; the risk of developing complications during the course of IE, such as the appearance of encephalopathy and hemorrhages, is

also high.

A further result worth emphasizing is the lack of differences in the appearance of anatomical complications of IE, although the group with liver disease had a higher rate of involvement of the tricuspid valve, a site less likely to lead to complications. This could be explained by the low incidence of appearance of these complications, making statistically significant differences unlikely.

We should also stress that the main cause of death in patients with liver disease is sepsis. Chronic liver diseases undoubtedly produce a state of immunodepression, which underlies the lack of efficacy of normal antibiotic treatments. Furthermore, because the frequency of heart failure is low in patients with liver disease, there are fewer deaths due to heart failure than normal in this population. These differential characteristics influence the current tendencies of presentation of IE. Years ago it was diagnosed in very small groups of patients but today diagnosis of IE is common, although we know little of its progression.

The most important finding of this study is, however, that we have been able to show that the presence of chronic liver disease is a predictive factor independent of the poor prognosis of patients with IE. We should point out that although patients without liver disease are older, with more heart failure and more prosthetic endocarditis, they do not have a higher initial mortality than patients with liver disease. As a first approximation, comparison using the log-rank test did not show significant differences between the two groups, although both curves appear to diverge from the start. The small sample size could be responsible for the lack of statistical significance, but because of the low incidence of this disease, it is unusual to find a larger group of patients. However, liver disease is an independent predictor of mortality in the Cox proportional hazards analysis. In the univariate analysis, the presence of chronic liver disease diagnosed prior to IE was not a factor that increased the risk of mortality. But when the age of the patients, a variable clearly related to prognosis of the subjects with IE, was introduced into a bivariate analysis, the presence of liver disease significantly increased the risk of mortality. When an analysis was done with all variables that might affect the survival of these patients, the only ones to remain statistically significant were age, presence of chronic liver disease and the development of heart failure. According to the adjusted model, the presence of liver disease increases the risk of mortality in the long term in patients with IE by approximately two and a half times compared to those without liver disease. We emphasize that the presence of chronic liver disease remained statistically significant, even when it was introduced as a covariate for the development of heart failure. This is one of the

most important determinants in the prognosis of patients with IE and its appearance was less common in the group of patients with liver disease. In previous studies, chronic liver disease had already been identified as a factor for predisposition to IE,¹⁸ but the change that this disease makes to prognosis of such patients had not been studied.

This is the first time that this result is reflected in an extensive patient population with long-term follow-up. We therefore believe that our results should influence the management of these patients, with the adoption of more aggressive therapeutic measures such as the administration of longer cycles of antibiotic.

LIMITATIONS

As mentioned previously, the small number of patients included in the study could be a limiting factor for obtaining statistically significant differences. Nevertheless, because of the low prevalence of this disease, the only way to include more patients would be through multicenter studies. Another factor to bear in mind is that our center is a reference hospital for cardiology and cardiovascular surgery, which probably means that the patients included in the study have more serious signs and symptoms and a worse prognosis than the average population affected by this disease.

CONCLUSIONS

Infectious endocarditis presents a series of differential characteristics when it affects patients with chronic liver disease. The presence of chronic liver disease is responsible for a worse prognosis in patients with IE, with a two-and-a-half fold increase in the risk of death. Because of this finding, we should consider patients with chronic liver disease and IE as high risk.

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