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Original article

Granulomatous liver disease in a referral center in Mexico city

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ABSTRACT

Introduction and Objectives: Up to 15 % of liver biopsies may reveal granulomas. The underlying causes vary geographically, with marked differences between high- and low-middle-income countries. No studies have examined the etiology of granulomatous liver disease (GLD) in Mexico. This study aims to describe the etiologic profile and clinical outcomes of patients diagnosed with GLD at a tertiary care center in Mexico.
Materials and Methods: Retrospective cohort study of patients diagnosed with GLD by liver biopsy between 2001 and 2017.
Results: We identified 133 patients with GLD. The most common causes were infectious diseases (36.1 %, *n* = 48; including 22 mycobacterial infections), foreign body reactions (21.1 %, *n* = 28), and autoimmune disorders (15.0 %, *n* = 20). The overall 6-month survival probability was 90.9 % (95 % confidence interval [CI], 86–95 %), declining to 87.5 % (95 % CI, 82–93 %) at 12 months. Patients with autoimmune etiologies had the best prognosis (100 % survival at 6 and 12 months). In contrast, patients with neoplastic GLD had the poorest outcomes, with survival probabilities of 72.7 % (95 % CI, 50.6–100 %) at 6 months and 63.6 % (95 % CI, 40.7–99.5 %) at 12 months. Patients with idiopathic GLD had a favorable short-term prognosis, with a 12-month survival probability of 92 %.
Conclusions: In this cohort, infectious diseases were the most common cause of GLD. Prognosis varied by etiology, with idiopathic cases showing favorable short-term outcomes and neoplastic cases exhibiting poor survival rates.
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1. Introduction

Hepatic granulomas result from a cellular immune response to poorly degraded antigens and are characterized by the accumulation of macrophages and other inflammatory cells [1,2]. They are identified in up to 15 % of liver biopsies [2]. Although they may represent

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incidental findings, their presence can aid in diagnosing underlying hepatic or systemic diseases [2,3].

Several histologic patterns of liver granulomas have been described, some associated with specific underlying conditions [2]. For example, epithelioid necrotizing granulomas are commonly linked to mycobacterial and fungal infections, as well as to nocardiosis, while epithelioid non-necrotizing granulomas are associated with adverse drug reactions, sarcoidosis, hepatitis C, and primary biliary cholangitis (PBC). Microgranulomas are typically regarded as nonspecific responses to liver injury; fibrin ring granulomas are most frequently observed in Q fever but may also occur in other infectious etiologies (e.g., toxoplasmosis), and noninfectious conditions (e.g., Hodgkin's disease); and lipogranulomas are primarily associated with steatohepatitis [2,4,5]. Additionally, the location of these granulomas may also aid in identifying an underlying etiology [2,3,5].

The predominant causes of granulomatous liver disease (GLD) worldwide include sarcoidosis, tuberculosis, autoimmune etiologies (e.g., PBC), and idiopathic GLD [2,3,5,6]. However, the leading etiologies vary by geographic region [2,5]. In high-income countries, autoimmune conditions—particularly PBC—and sarcoidosis are more frequently observed [2,7–11] In contrast, infectious causes, such as tuberculosis, predominate in low- and middle-income settings [2,3,5,6,12]. Notably, up to 50 % of cases remain without an identifiable cause and are ultimately classified as idiopathic GLD [2,13].

Given these regional differences, it is essential to identify the most common causes of GLD in Mexico. Understanding the underlying etiologies of GLD can guide diagnostic approaches, inform treatment decisions, and ultimately improve patient outcomes. Therefore, this study aimed to determine the etiologies, clinical characteristics, and outcomes of patients diagnosed with GLD in a tertiary care center in Mexico City.

2. Materials and Methods

2.1. Setting, participants, and study design

We conducted a retrospective cohort study at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ), a national referral center for liver and infectious diseases within the National Institutes of Health. We included all adult patients who underwent liver biopsies between January 2001 and December 2017 and whose histopathology reports mentioned the term granuloma or related descriptors such as GLD. Additionally, cases in which the presence of liver granulomas could not be confirmed upon secondary review by the pathologists (FAOE and MBB) were excluded, provided histopathology material was available for revision. Finally, we documented the patient's vital status at 6 and 12 months after diagnosis.

2.2. Study variables and data sources

We reviewed patients' medical records to collect baseline characteristics, including demographic information (i.e., sex, age, place of birth, and residence) and comorbidities. A patient was considered immunocompromised if they had a history of HIV infection, solid organ transplantation, malignant neoplasm, long-term steroid use (i.e., equivalent to ≥10 mg of prednisone daily for more than two weeks), use of any other immunosuppressive drug, primary immunodeficiency or neutropenia of any cause.

Additionally, we collected baseline data on symptoms (e.g., abdominal pain, jaundice, fever, nausea, or vomiting) and laboratory test results (e.g., complete blood count, liver function tests [LFTs], and serology results [e.g., viral hepatitis, Q fever, antinuclear antibodies], along with other microbiology laboratory results). Liver biopsies were reviewed by FAOE and MBB, who classified granulomas by location (i.e., periportal, centrilobular, sinusoidal, or subcapsular) and type (i.e., epithelioid, lymphohistiocytic, microgranuloma, lipogranuloma, or ring granuloma). Finally, we recorded the definitive clinical diagnosis and classified each case into one of six categories based on the underlying cause: idiopathic, infectious, autoimmune, foreign body, neoplastic, or other.

2.3. Statistical analysis

We used descriptive statistics—medians with interquartile ranges (IQR) and counts with proportions—to summarize the baseline characteristics of the study population, both overall and by their etiology. Baseline clinical and demographic characteristics were compared among the six groups using the Pearson's chi-squared test or the Kruskal-Wallis test as appropriate. We used the Kaplan-Meier estimator to assess overall survival and generated survival curves to visualize differences among groups. All analyses were conducted using R (version 4.1.0, R Foundation for Statistical Computing, Vienna, Austria, 2022).

2.4. Ethics approval

The Institutional Ethics and Research Committee approved this study and waived informed consent (protocol number INF-2896–19–20–1).

3. Results

3.1. Baseline characteristics

A total of 2529 liver biopsies were performed during the study period, of which 174 mentioned the term granuloma or related descriptors in the pathology report. Forty-one cases were excluded after slide review failed to confirm the presence of granulomas. The final study population comprised 133 patients (5.3 % of all liver biopsies), most of whom resided in central Mexico (Fig. 1).

The median age was 46 years (IQR, 32–57), and 56 % were male (Table 1). Comorbidities included diabetes mellitus in 9.2 % of patients, hypertension in 9.9 %, and 29 % were considered immunocompromised. Among the latter, 41.0 % had an underlying neoplasia, 23.1 % were living with HIV, 17.9 % were receiving steroids or other immunosuppressive drugs, 12.8 % had a history of solid organ transplantation, and 5.1 % had other causes of immunosuppression.

The most frequent presenting symptoms were fever (53 %), abdominal pain (53 %), and jaundice (46 %). Seventy percent of patients exhibited a cholestatic pattern, while 14 % had normal LFTs at presentation. The most common histologic types were epithelioid granulomas (40 %), lymphohistiocytic (38 %), and microgranulomas (23 %), and they were most often located near the portal triad (79 %) (Table 2).

3.2. Etiology of GLD

The most common causes of GLD were infectious diseases (n = 48, 36.1 %), foreign body reactions (n = 28, 21.1 %), and autoimmune disorders (n = 20, 15.0 %). Neoplastic etiologies accounted for 11 cases (8.3 %), other causes for 12 (9.0 %), and the remaining 14 patients (10.5 %) were classified as idiopathic GLD.

3.2.1. Infectious etiologies of GLD

Among the 48 patients with an infectious etiology, 22 (45.8 %) had mycobacterial infections—most commonly *Mycobacterium tuberculosis* (n = 17), followed by *M. avium* complex (n = 3), and *M. bovis* (n = 2). Other bacterial infections were identified in 15 patients (31.3 %), including localized abscesses (n = 7), Q fever (n = 6), and brucellosis (n = 2). Viral infections were found in six patients (hepatitis C virus, n = 4; Epstein-Barr virus, n = 1; cytomegalovirus, n = 1). Fungal infections occurred in two cases (*Histoplasma capsulatum* and *Geotrichum capitatum*), and parasitic infections in three (*Echinococcus*

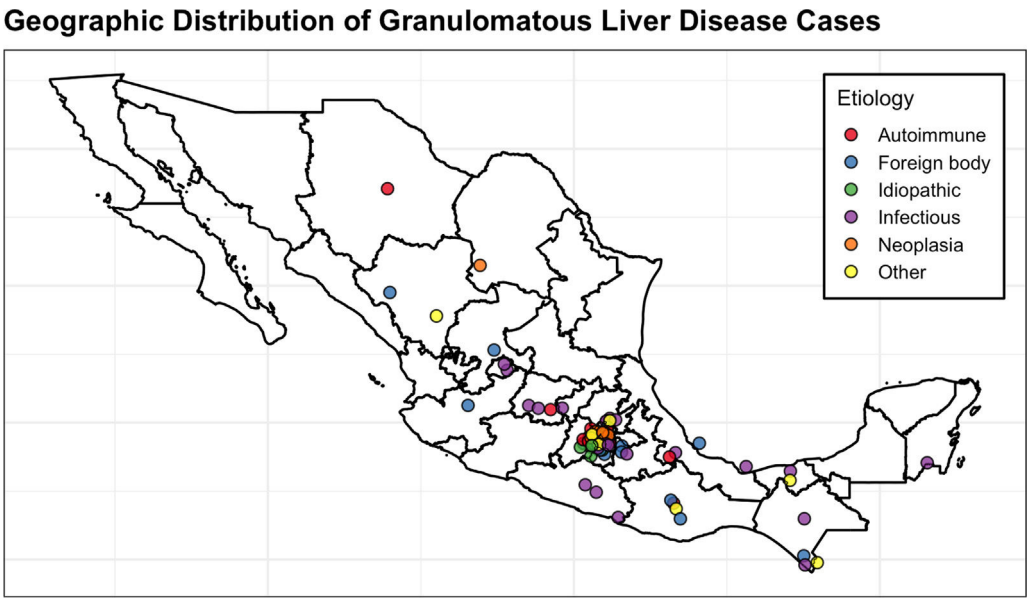

Fig. 1. Geographic distribution of the 133 patients diagnosed with granulomatous liver disease at a referral center in Mexico City (2001–2017).

Table 1
Baseline characteristics of 133 patients diagnosed with granulomatous liver disease at a referral center in Mexico City (2001–2017), overall and by the underlying etiology.

	Overall *N* = 133	Autoimmune disorders *N* = 20	Foreign body reactions *N* = 28	Idiopathic GLD *N* = 14	Infectious diseases *N* = 48	Neoplasia *N* = 11	Other etiologies *N* = 12	P-value†
Demographic characteristics								
Age (years); median (IQR)	46 (32 –57)	46 (34–54)	48 (32–58)	37 (29–52)	42 (32–58)	61 (48–68)	46 (38–53)	0.23
Sex (male); n (%)	75 (56)	16 (80)	21 (75)	5 (36)	19 (40)	7 (64)	7 (58)	0.004
Comorbidities								
Diabetes mellitus; n (%)	12 (9.2)	2 (10)	1 (3.6)	1 (7.1)	5 (11)	1 (9.1)	2 (17)	0.80
Hypertension; n (%)	13 (9.9)	3 (15)	3 (11)	1 (7.1)	3 (6.5)	1 (9.1)	2 (17)	0.79
Immunocompromised; n (%)	39 (29)	4 (20)	5 (18)	4 (29)	13 (27)	9 (82)	4 (33)	0.006
Connective tissue diseases; n (%)	10 (7.6)	6 (30)	1 (3.6)	0 (0)	2 (4.3)	0 (0)	1 (8.3)	0.015
Hepatopathy; n (%)	16 (12)	4 (20)	3 (11)	0 (0)	8 (17)	0 (0)	1 (8.3)	0.37
ESKD; n (%)	4 (3.1)	0 (0)	0 (0)	1 (7.1)	2 (4.3)	1 (9.1)	0 (0)	0.37
Cancer; n (%)	16 (12)	1 (5.0)	7 (25)	0 (0)	2 (4.3)	5 (45)	1 (8.3)	0.001
Liver transplant; n (%)	4 (3.0)	0 (0)	1 (3.6)	0 (0)	2 (4.2)	0 (0)	1 (8.3)	0.84
Others; n (%)	38 (29)	5 (25)	11 (39)	8 (57)	11 (24)	2 (18)	1 (8.3)	0.072
HIV; n (%)	10 (7.7)	0 (0)	0 (0)	2 (14)	6 (13)	1 (9.1)	1 (8.3)	0.14
Charlson Comorbidity Index; median (IQR)	1 (0–3)	1 (1–1)	0.5 (0–4)	1 (0–3)	2 (0–4)	5 (2–8)	0.5 (0–1)	0.048
Symptoms								
Fever; n (%)	65 (53)	4 (25)	11 (46)	10 (71)	33 (72)	4 (36)	3 (27)	0.003
Jaundice; n (%)	58 (46)	6 (38)	17 (68)	6 (43)	18 (38)	4 (36)	7 (58)	0.18
Abdominal pain; n (%)	66 (53)	9 (53)	18 (72)	4 (29)	21 (46)	7 (64)	7 (58)	0.13
Nausea or vomiting; n (%)	35 (29)	6 (35)	10 (42)	2 (15)	10 (22)	4 (36)	3 (25)	0.56
Laboratory tests								
Leukocytes (10^3/dL); median (IQR)	6.5 (4.5–9.0)	5.8 (4.4–6.8)	7.6 (5.7–9.3)	7.0 (4.2–11.9)	6.0 (4.5–9.0)	5.8 (5.0–7.4)	7.0 (6.0–8.5)	0.56
Neutrophils (%); median (IQR)	65 (53–76)	62 (51–67)	67 (52–76)	70 (50–83)	69 (62–81)	61 (54–70)	59 (46–65)	0.012
ALT (IU/L); median (IQR)	50 (26–102)	84 (46–238)	62 (28–111)	42 (24–98)	36 (22–79)	29 (18, 54)	58 (42, 98)	0.046
AST (IU/L); median (IQR)	54 (31–113)	96 (48–182)	64 (34–119)	49 (28–95)	50 (28–83)	38 (19–142)	50 (32–117)	0.23
Alkaline phosphatase (IU/L); median (IQR)	203 (116–428)	287 (141–819)	210 (144–323)	219 (114–280)	172 (100–424)	157 (102–371)	185 (138–264)	0.53
Total bilirubin (mg/dL); median (IQR)	1.1 (0.6–3.2)	0.9 (0.6–3.8)	2.0 (0.9–5.1)	1.1 (0.7–2.9)	0.9 (0.6–1.8)	0.8 (0.4–1.0)	1.7 (0.8–10.8)	0.12
INR; median (IQR)	1.10 (1.00–1.20)	1.00 (0.93–1.00)	1.10 (1.00–1.23)	1.10 (1.00, 1.11)	1.12 (1.04–1.37)	1.10 (1.00–1.14)	1.10 (1.00–1.19)	0.007
Pattern of liver damage in LFTs								
Cholestatic; n (%)	91 (70)	15 (79)	20 (77)	9 (64)	33 (69)	7 (64)	7 (58)	0.05
Hepatocellular; n (%)	15 (12)	3 (16)	2 (7.7)	0 (0)	8 (17)	1 (9.1)	1 (8.3)	
Mixed; n (%)	6 (4.6)	0 (0)	2 (7.7)	1 (7.1)	0 (0)	0 (0)	3 (25)	
Normal LFTs; n (%)	18 (14)	1 (5.3)	2 (7.7)	4 (29)	7 (15)	3 (27)	1 (8.3)	

Abbreviations: ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; ESKD: End-stage kidney disease; HIV: Human Immunodeficiency Virus; INR: International Normalized Ratio; IQR: Interquartile range; LFTs: Liver function tests.
† Pearson's chi-squared test or Kruskal-Wallis test.
Note: Percentages are based on available data. Denominators may vary due to missing values for some variables.

Table 2
Histological characteristics of granulomas in 133 patients diagnosed with granulomatous liver disease at a referral center in Mexico City (2001–2017), overall and by underlying etiology.

	All *N* = 133	Autoimmune disorders *N* = 20	Foreign body reactions *N* = 28	Idiopathic GLD *N* = 14	Infectious diseases *N* = 48	Neoplasia *N* = 11	Other etiologies *N* = 12
Not available	16 (12 %)	4 (20%)	1 (4 %)	2 (14 %)	7 (14.6 %)	0 (0 %)	2 (17 %)
By histological characteristics							
Epithelioid	47 (40 %)	5 (31 %)	8 (30 %)	8 (67 %)	21 (51 %)	4 (36 %)	1 (10 %)
Lymphohistiocytic	45 (38 %)	7 (44 %)	13 (48 %)	3 (25 %)	12 (29 %)	4 (36 %)	6 (60 %)
Microgranuloma	27 (23 %)	5 (31 %)	7 (26 %)	5 (42 %)	4 (9.8 %)	3 (27 %)	3 (30 %)
Lipogranuloma	9 (7.7 %)	0 (0 %)	0 (0 %)	3 (25 %)	5 (12 %)	0 (0 %)	1 (10 %)
Fibrin-ring granuloma	1 (0.9 %)	0 (0 %)	0 (0 %)	0 (0 %)	1 (2.4 %)	0 (0 %)	0 (0 %)
By location							
Portal	93 (79 %)	15 (94 %)	21 (78 %)	9 (75 %)	31 (76 %)	8 (73 %)	9 (90 %)
Sinusoidal	54 (46 %)	1 (6.2 %)	13 (48 %)	7 (58 %)	26 (63 %)	3 (27 %)	4 (40 %)
Centrolobulillar	13 (11 %)	1 (6.2 %)	4 (15 %)	2 (17 %)	4 (9.8 %)	1 (9.1 %)	1 (10 %)
Subcapsular	5 (4.3 %)	0 (0 %)	0 (0 %)	0 (0 %)	4 (9.8 %)	1 (9.1 %)	0 (0 %)

Note: Some patients had more than one type of granuloma, resulting in a total percentage greater than 100 %.

granulosus, Ascaris lumbricoides, and one in which the exact species could not be identified).

3.2.2. Non-infectious etiologies of GLD

Among the 71 patients with a non-infectious etiology, 28 (39.4 %) had foreign body reactions, often due to retained postoperative material, such as surgical sutures. Autoimmune causes were identified in 20 patients (28.2 %), including nine with overlapping PBC and autoimmune hepatitis, eight with PBC, and three with autoimmune hepatitis. A neoplastic etiology was identified in 11 individuals (15.5 %), including lymphomas (*n* = 3), hepatocellular carcinoma (*n* = 2), and a variety of other malignancies such as neuroendocrine tumor, cystic adenoma, cholangiocarcinoma, and pancreatic, gallbladder, and prostate adenocarcinomas. The remaining 12 patients (16.9 %) had other etiologies, including nonalcoholic steatohepatitis (*n* = 5), drug-induced liver injury (*n* = 5), sarcoidosis (*n* = 1), and familial intrahepatic cholestasis (*n* = 1).

3.2.3. Idiopathic GLD

Fourteen patients were classified as having idiopathic GLD. The median age was 37 years, and 64 % were female. Clinically, most presented with signs of a systemic inflammatory response, including fever (71 %) and leukocytosis (35 %). The majority of patients were suspected of having an infectious etiology and thus received antimicrobial therapy—most commonly antituberculosis drugs or doxycycline for suspected Q fever—with all but one patient responding favorably to treatment. The patient who did not respond was a 54-year-old woman with a history of renal transplantation, admitted with fever of unknown origin. A chest CT revealed a miliary pattern along with pleural and ileal wall thickening. Bronchoscopy and colonoscopy with biopsies and cultures were performed; however, all results were negative. A liver biopsy showed GLD suggestive of tuberculosis. She received antituberculosis therapy but, unfortunately, died with clinical suspicion of disseminated tuberculosis. No autopsy was performed.

3.3. Survival outcomes

The overall 6-month survival probability for the cohort was 90.9 % (95 % CI, 86–95 %), declining slightly to 87.5 % (95 % CI, 82–93 %) at 12 months (Fig. 2). Survival outcomes varied by etiology (Fig. 3). Patients with autoimmune GLD had the highest survival, with a 100 % probability at both 6 and 12 months. Similarly, only one death was recorded among patients with foreign body reactions, and it was attributed to an unrelated cause. In contrast, infectious etiologies were associated with lower survival rates: 82 % at 6 months (95 % CI, 73–94 %) and 80 % at 12 months (95 % CI, 70–93 %). The poorest outcomes were observed among patients with neoplastic GLD, with survival probabilities of 72.7 % (95 % CI, 50.6–100 %) at 6 months and 63.6 % (95 % CI, 40.7–99.5 %) at 12 months. Patients with idiopathic GLD had a 100 % survival rate at 6 months and 92.3 % (95 % CI, 78.9–100 %) at 12 months.

4. Discussion

The increasing number of liver biopsies has led to greater recognition of hepatic granulomas of various etiologies across different regions [2]. In our study, 5.3 % of liver biopsies revealed hepatic granulomas, consistent with reports from other large cohorts worldwide (1–15 %) [2,7,11].

Hepatic granulomas arise from two primary sources: infectious and non-infectious etiologies. In our cohort, the most common underlying causes were infectious diseases, primarily mycobacterial infections, which is consistent with findings from other emerging regions such as Iran and Pakistan [2,12,14,15]. In contrast, studies conducted in high-income countries such as Germany, Ireland, and Australia frequently report sarcoidosis and autoimmune diseases as the leading cause of hepatic granulomas, with PBC being one of the most frequent etiologies [2,10,16,17]. In our study, autoimmune disorders were the third most common cause of GLD, while, as expected, sarcoidosis—a disorder that predominantly affects Caucasian populations[18]—was very uncommon in our cohort, with only one patient diagnosed with this condition.

While higher transmission rates of certain infectious diseases such as tuberculosis may explain the increased prevalence of infections in

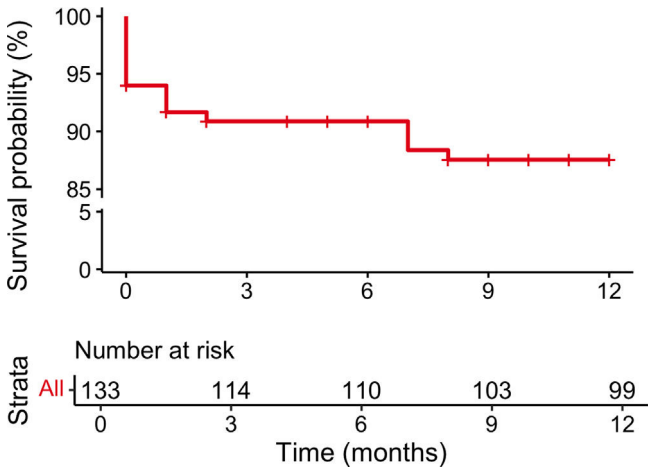

Fig. 2. Kaplan-Meier survival estimates among all 133 patients diagnosed with granulomatous liver disease at a referral center in Mexico City (2001–2017).

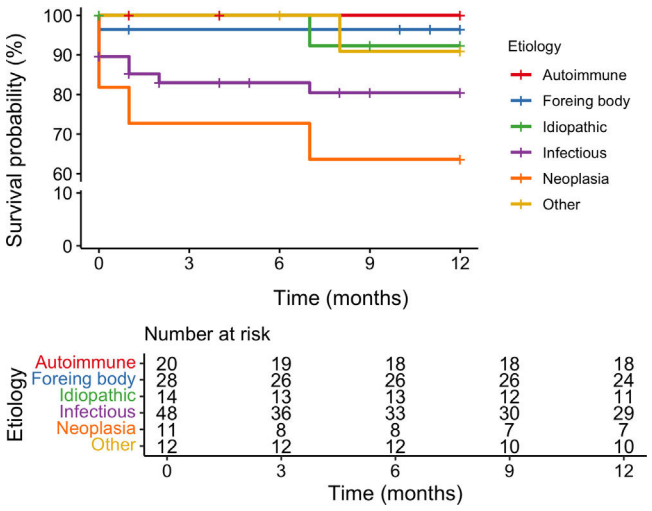

Fig. 3. Etiology-specific Kaplan-Meier survival estimates in patients diagnosed with granulomatous liver disease at a Mexico City referral center (2001–2017).

our cohort, the baseline characteristics of our study population could also have played a role—nearly one-third-of the cohort was considered immunocompromised. Therefore, the high prevalence of infectious causes of GLD should be interpreted with caution, as it may be partly influenced by referral bias.

Regarding overall survival, the prognosis was generally favorable, with a 6-month survival probability of 90.9 %, decreasing slightly to 87.5 % at 12 months. However, outcomes varied considerably by etiology: patients with autoimmune diseases had the highest survival (100 % at both 6 and 12 months), whereas those with neoplastic GLD had the lowest (63.6 % at 12 months), reflecting the progressive nature of malignancies. Notably, patients with idiopathic GLD had a 12-month survival rate of 92 %, consistent with findings from other studies [18].

It is also important to note that most patients with idiopathic GLD in our cohort—including the only patient in this group who died—had a strong clinical suspicion of an underlying infectious etiology. This contrasts with findings from high-income regions, where idiopathic cases are more often attributed to autoimmune diseases or sarcoidosis. As noted in the literature, idiopathic GLD may reflect the limitations of available diagnostic tools [19]. However, it may also correlate with the predominant etiologies in a given region. Therefore, a thorough evaluation —tailored to the clinical presentation— and careful exclusion of common infectious causes are essential before initiating treatment for autoimmune disorders in patients with an unknown cause of GLD in our setting. In addition, close clinical follow-up is recommended, as some patients may develop new symptoms that help clarify the underlying cause [18].

This study has several strengths but also some limitations. Among its strengths, it is the first report of GLD in Mexico and surrounding regions to provide valuable information that can guide the diagnostic approach to patients with hepatic granulomas. Additionally, our 17-year study period allowed us to compile a large case series. However, the single-center design may limit the generalizability of our findings. The retrospective nature of the study also relied on existing medical records, leading to some missing data. Furthermore, diagnostic techniques and medical management evolved over the study period, which may have influenced our results.

5. Conclusions

In conclusion, infectious diseases were the most common cause of GLD in this cohort. Patients with idiopathic GLD had a favorable short-term prognosis, whereas those with neoplastic etiologies had poor overall survival. Future multicenter studies with standardized data collection are warranted to obtain more generalizable results.

Declaration of interests

None.

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Author contributions

J.R.M., S.M.F.A., D.A.L., E.O.B., and A.P.L. conceived the project. D.A.L., R.C., and M.J.M.T. collected the data. A.O.M. conducted all analyses. J.R.M., S.M.F.A., E.O.B., and A.P.L. drafted the first version. E.O.B. prepared the final draft. A.O.M., D.A.L., M.B.V., O.F.A., B.M.B., D.K.S., J.S.O., E.O.B., and A.P.L. edited the first and final drafts. J.R.M., E.O.B., and A.P.L. take responsibility for the integrity and accuracy of this work.

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