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Original Article

Post-infantile Giant Cell Hepatitis: A Literature Review and Meta-analysis

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Abstract

Post-infantile giant cell hepatitis (PIGCH) is a rare disease entity in adults with a multifactorial etiology and widely variable clinical courses and outcomes. The factors associated with the worse outcomes of this disease entity are still unclear. We identified 68 PIGCH patients by searching PubMed and performed meta-analysis. Among the 68 patients, 32% of the cases were associated with autoimmune disorders, followed by 21% associated with viral infections, 10% with medication, and 7% with malignancy. Twenty-four percent of the patients had more than one etiological factor, and 6% had other uncommon etiologies or an etiology that could not be identified. At the time of this report, 17 patients had died of the disease (poor outcome), and 51 patients remained alive with the disease (good outcome). Compared to the patients with a good outcome, the patients with a poor outcome were characterized by older age, lower levels of platelets and albumin, higher level of total bilirubin, and a diffuse distribution pattern of giant cells in the liver. There were no differences in gender distribution, aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, etiological distribution, or other histological features, including interface hepatitis, necrosis, lobular inflammation, portal inflammation, cholestasis, or fibrosis. Further studies would be needed to better understand the disease mechanisms and unmask any additional etiological factors and targeted therapies.

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Introduction

Neonatal giant cell hepatitis is a common cause of cholestasis in infants. It is characterized histologically by the formation of syncytial hepatic giant cells (hepatocytes with abundant cytoplasm and more than three nuclei)[1] and hepatitis (lobular disarray, lobular inflammation, Kupffer cell hypertrophy, and hepatocyte spotty necrosis).[2] Etiologies related to neonatal giant cell hepatitis include hypopituitarism, biliary atresia, Alagille syndrome, bile salt defects, and severe hemolytic disease of the newborn. However, a significant number of neonatal giant cell hepatitis remains idiopathic.[3,4] When the disease entity occurs in adults, it is an extremely rare condition known as post-infantile giant cell hepatitis (PIGCH), or syncytial giant cell hepatitis. Due to the differences in the hepatocyte maturity of the metabolic enzyme systems,[5] regenerative activity,[6] and the spectrum of background liver diseases, giant cell hepatitis in adults is considered a separate disease entity. The clinical course of PIGCH is widely variable ranging from minimal symptoms without major clinical implications to cirrhosis or to liver failure that is often fatal despite standard clinical care. Here we identified 68 cases in the literature and tried to characterize the clinical, laboratory, and histological features by meta-analysis to identify the factors associated with a poor outcome.

Materials and methods

Case identification and selection

We conducted a comprehensive literature search in PubMed in January 2022, using the terms "giant cell hepatitis", "giant cell change" AND "liver", and "giant cell transformation" AND "liver". Only original articles were retrieved and reviewed. A case was selected and included in this study if: (1) The patient's age at the disease onset was older than or equal to 18 years, (2) the article had information of clinical, laboratory, histology, and disease outcomes, and (3) the article was published in a peer-reviewed journal in English. The excluded criteria included: (1) Important information was missing, (2) no full text was available, and (3) irrelevant articles.

Data extraction

The following data were extracted from the original articles or pathological descriptions, if available: title, journal information, country/region of the corresponding author, age, gender, clinical symptoms and signs, laboratory results, histology, outcome, and length of the follow-up. All of the case entries were assessed by author JJ. The study flow diagram is shown in Figure 1. The meta-analysis was in compliance with the PRISMA guidelines, and a total of 68 patients qualified and were included in this series.

Keywords: Post-infantile giant cell hepatitis; Syncytial giant cell hepatitis; Autoimmune hepatitis; Liver transplantation; Virus.

Abbreviations: ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; CLL, chronic lymphocyte leukemia; EBV, Epstein-Barr virus; HCV, hepatitis C virus; HHV-6, human herpes virus-6; PIGCH, post-infantile giant cell hepatitis.

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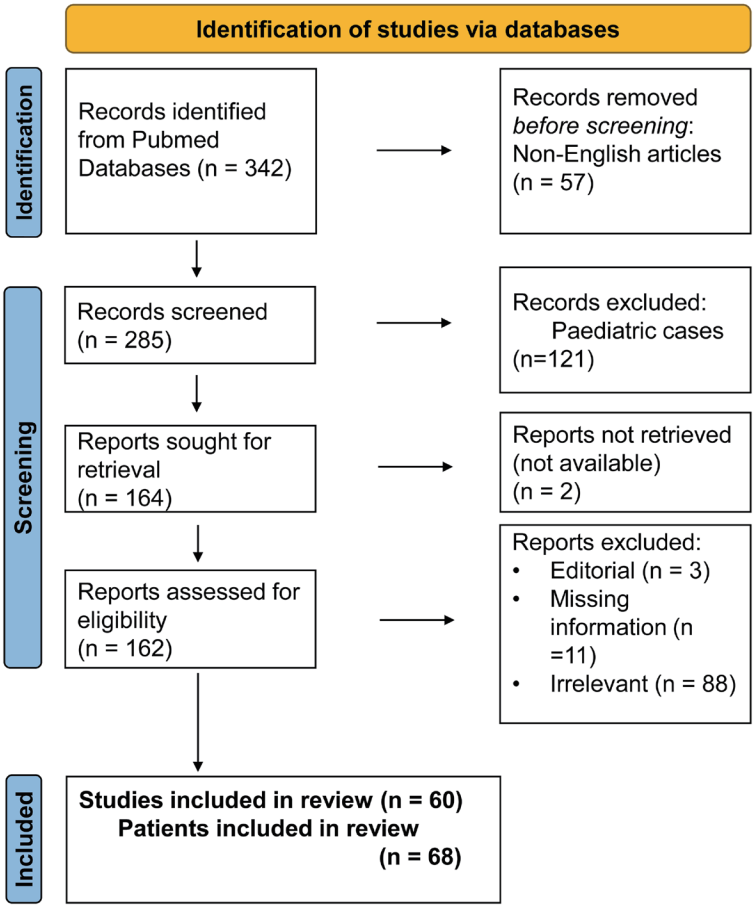

Fig. 1. The selection process of post-infantile giant cell hepatitis.

Statistical analysis

Demographic and clinical parameters were compared between the deceased and living patients at the time of the report using two-tailed student's *t*-tests for continuous variables, and Fisher exact or chi-squared tests for the categorical variables as indicated. A *p*-value less than 0.05 was considered statistically significant.

Results

Clinical, laboratory and histological features

Among the 68 patients, the distribution of the patients' age ranged from 18 to 79 years with a median of 41.5 years. The ratio of male to female was 1.3:1 (male 57.4%; female 42.6%). Of the cases, 44.1% were from Europe, 33.8% were from America, and 22.1% were from Asia. The leading symptoms/signs were jaundice (n = 44), followed by fatigue (n = 29), hepatomegaly (n = 22), abdominal pain/tenderness (n = 14), and splenomegaly (n = 14).

All the patients with liver functional test data had elevated aminotransferase. The median levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were 500 U/L and 466.5 U/L with a range of 40–5,350 U/L and 39–5,609 U/L, respectively. 91.1% of the patients had elevated total bilirubin with a median value of 10.6 mg/dL (range: 0.7–42 mg/dL). The median level of albumin was 3.0 g/dL (range: 2.2–4.1 g/dL). The percentage of patients with positive antinuclear antibodies, anti-smooth muscle antibodies, and anti-mitochondrial antibodies was 60%, 38.6%, and 20.5%, respectively.

The distribution pattern of the multinucleated giant cells in the liver was specified in 27 PIGCH patients with eight cases predominantly at Zone 1, one at Zone 2, eight at Zone 3, eight with a diffuse distribution pattern, one at both Zones 2 and 3, and one case with a "no preference" pattern. Those giant cells could contain up to 30 nuclei[7] with an abundant and eosinophilic cytoplasm, which could contain eosinophilic granules, Mallory-Denk bodies, brown granules, and/or bile pigment (Figs. 2a, b).[8–15] Acidophilic degeneration[9] and giant cell necrosis were sometimes observed with the neutrophilic reaction as well.[12,16,17] Among the 51 cases with information of fibrosis in the liver histology, seven had no fibrosis and 44 had a different degree of fibrosis, among which 11 reached cirrhosis. Portal inflammation and lobular inflammation were mentioned in 34 and 19 cases, respectively. Thirty-seven cases had a variable amount of necrosis. Interface hepatitis was present in 21 cases, and 24 cases had histological features of cholestasis. Ductular reaction (n = 8), ballooning (n = 7), steatosis (n = 5), Councilman (acidophilic) body (n = 4), Mallory-Denk body (n = 3), and Kupffer cell hyperplasia (n = 3) were features infrequently encountered.

Distribution of the etiology

With regard to the etiological factors, 32% of the cases were associated with autoimmune disorders, 21% were associated with viral infections, 10% were associated with medication

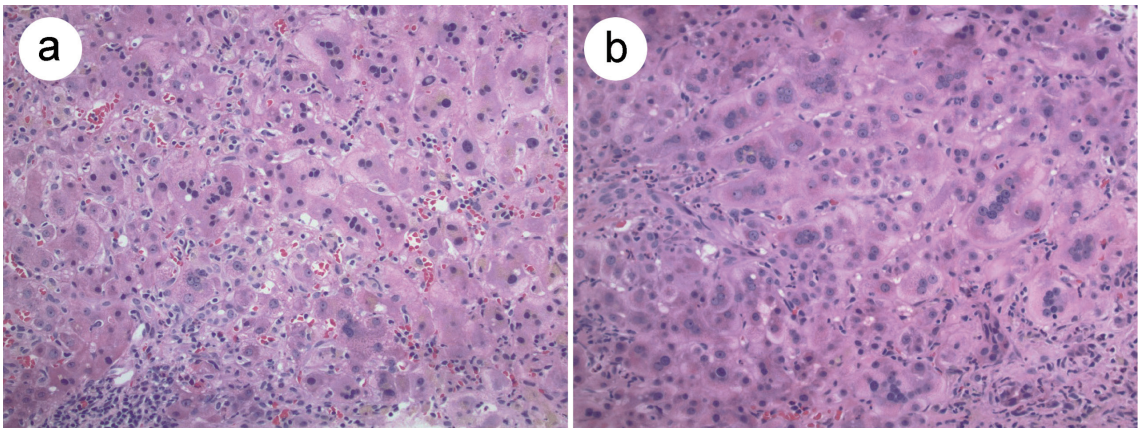

Fig. 2. Representative images of post-infantile giant cell hepatitis. (a) Giant cell hepatitis in a liver with chronic lymphocytic leukemia. (b) Giant cell hepatitis in a liver with autoimmune hepatitis. (Hematoxylin and eosin stain, original magnification 200×).

(including herbal products or dietary supplement intake), 7% were associated with malignancy, 24% had more than one etiological factor, and 6% had other uncommon etiologies or an etiology that could not be identified at the time of publication (Fig. 3).

Among the autoimmune disorders associated with PIGCH, autoimmune liver diseases were the most common, including autoimmune hepatitis (type I or II),[12,18–30] primary sclerosing cholangitis,[7,31] and primary biliary cholangitis.[10] Other autoimmune conditions included systemic lupus erythematosus,[32,33] Graves' disease,[34] undifferentiated connective tissue disease,[35] and polyarteritis nodosa.[20] Some cases of PIGCH had features of autoimmune disorders (e.g., elevated autoantibodies) and improved after immunosuppressive therapy without having a specific autoimmune disease diagnosed.[11,36]

Viruses associated with PIGCH included hepatitis C (HCV),[15,16,29,37–39] human immunodeficiency virus (HIV),[16,28,39] human herpes virus-6 (HHV-6),[40] cytomegalovirus (CMV),[14,41,42] Epstein-Barr virus (EBV),[43,44] herpes simplex virus (HSV),[29] paramyxoviruses,[8,33,43,45] hepatitis A,[38,46,47] hepatitis B,[38] and hepatitis E.[48,49]

In addition to medications, such as clometacin,[50] diclofenac,[51] doxycycline,[11,17] amoxicillin/clavulanate,[12] dehydrocholic acid,[11] and testosterone analogue,[52] herbal remedies,[53–55] and dietary supplements[56] were also reported to have an association with PIGCH. The most commonly associated malignancy with PIGCH appeared to be chronic lymphocyte leukemia (CLL).[37,43,44,51,57–62] In addition, other malignancies seen in patients with PIGCH included Hodgkin's lymphoma, papillary thyroid carcinoma,[63] anaplastic carcinoma,[58] and primary myelofibrosis.[51]

Some patients had more than one etiology, including autoimmune disorder and a viral infection,[28,29,33] autoimmune disorder and medication,[11] CLL with autoimmune hemolytic anemia, and CLL with a viral infection. Singh *et al*. reported a case of PIGCH developed in a patient with autoimmune hepatitis in the setting of acute bacterial infection and recent use of hepatotoxic medications amoxicillin/clavulanate.[12] Another case of PIGCH developed in a patient with myelofibrosis and severe autoimmune hepatitis, which was probably triggered by diclofenac administration.[51]

Other rare conditions, which had been seen concomitantly with PIGCH, included Rosai-Dorfman disease,[64] necrobiotic

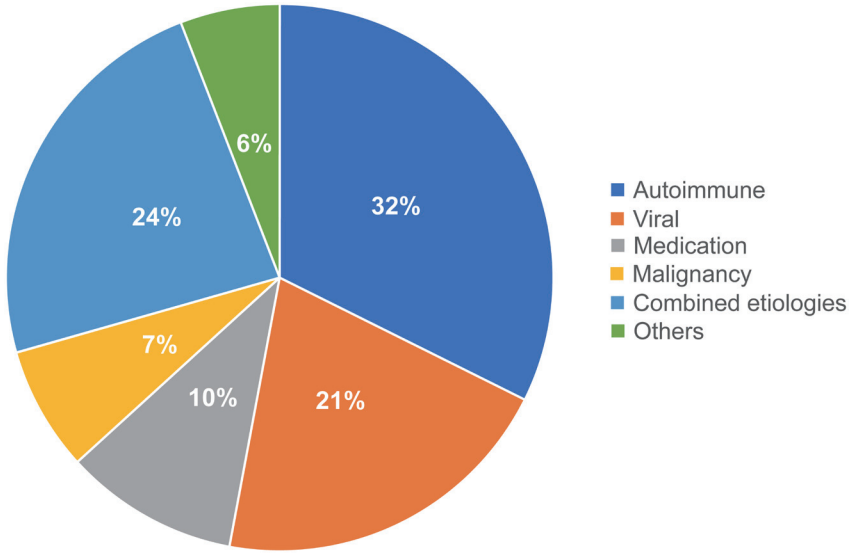

Fig. 3. Frequency of the etiologies of post-infantile giant cell hepatitis.

xanthogranulomatous disease,[65,66] and hypereosinophilia.[67] There were still, however, cases without any underlying process that could be identified despite an extensive workup.[68,69]

Clinical, laboratory, and histological features associated with the worse outcome

Seventeen patients had already passed away at the time of the report, 13 of these died of the deterioration of liver disease, while four died of non-liver related etiology (e.g., complications of CLL,[37] brain hemorrhage,[20] and pneumonia[7,33]). Fifty-one patients were alive at the time of the report, among whom 40 had significant improvement, seven had disease progression and survived after transplantation, and four patients had stable disease. Most of the improvements were based on clinical and/or biochemical improvements. The reduction or elimination of giant cells,[11,16,18,19,32,33,40] decreased inflammation,[23,33] or even regression of fibrosis[26] was documented to a less extent.

We compared the clinical, laboratory, and histological features of the PIGCH patients with a poor (deceased) versus good (living) outcome. Patients with a poor outcome had a significantly lower platelet count (median value: 126 × 10^9/L vs 207 × 10^9/L; $p = 0.04$), lower albumin concentration (median value: 2.7 g/dL vs 3.1 g/dL; $p = 0.012$), higher total bilirubin levels (median value: 18.0 mg/dL vs 8.4 mg/dL; $p = 0.022$) and were more likely to have a diffuse distribution pattern of giant cells (80% vs 18.2%; $p = 0.017$) than those of patients with a good outcome. There was also a trend of older age (median value: 60 vs 39 years; $p = 0.067$) and lower total protein level (5.5 g/dL vs 6.8 g/dL; $p = 0.056$) without reaching statistical significance. There were no differences in gender distribution, other liver function tests (aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase), etiological distribution, or other histological features (interface hepatitis, necrosis, lobular inflammation, portal inflammation, cholestasis, or fibrosis) between the two groups. The detailed comparison is summarized in Table 1.

Discussion

PIGCH is a very rare disease entity in adults with an estimated incidence ranging from 0.1% to 0.25%[47,70] and a multifactorial etiology. Consistent with previous reports,[1,70] autoimmune conditions, especially autoimmune liver diseases, remained the most common etiology. Many viruses, such as HCV, HIV, HHV-6, CMV, EBV, HSV, and paramyxoviruses were reported to be associated with PIGCH.[71] The most detailed studies were about HHV-6 and paramyxovirus. The association of HHV-6 with PIGCH was described in a liver transplantation recipient, who had a latent infection of an HHV-6B variant while receiving a liver from a donor with a latent infection of an HHV-6A variant, and developed PIGCH. HHV-6A (but not HHV-6B) was detected in the plasma, the affected liver tissue, and the syncytial giant cells, but the virus disappeared at the resolution of syncytial giant cell hepatitis.[40] In addition, HHV-6 was reported to induce giant cell formation in bile ductular and gastroduodenal epithelium.[72] The association of PIGCH with paramyxovirus was reported by finding intracytoplasmic paramyxoviral nucleocapsids by electron microscopy.[8] Although paramyxovirus and a paramyxovirus-like virus associated with PIGCH were also reported by other groups,[33,45] this theory was challenged[73,74] since the virus-like particles were possibly a microtubular aggregate[75] or endoplasmic reticulum in injured and/or stimulated cells.[76]

Multinucleated hepatocytes were also described in patients treated with certain medications or exposed to certain chemicals, including para-aminosalicylic acid,[77] methotrexate,[78] 6-mercaptopurine,[79] chlorpromazine,[80] and vinyl chloride.[81] The list kept expanding with microdantin, ranitidine, omeprazole, moxifloxacin, plaquenil, and chromium picolinate being recently added.[70] These agents do not seem to be related to any chemical structures, but many of them are recognized as "nuclear poisons" by interrupting the DNA and RNA synthesis, proliferation, and mitosis. Furthermore, although these agents were initially considered "natural" and safe, herbal remedies[53–55] and dietary supplements[56] associated with giant cell hepatitis have been reported. Notably, herbal remedies/dietary supplements as the cause for PIGCH might have been underestimated due to the fact that patients might not have reported their consumption on the conventional history taking.

The most commonly associated malignancy with PIGCH appears to be CLL. PIGCH can develop not only in advanced, pretreated patients,[37,59] but also in patients with a relatively indolent course.[60,61] Patients with CLL have a 5–10% risk of developing autoimmune complications.[62] The most common of them is autoimmune hemolytic anemia.[57] CLL patients also have profound immune defects, thus rendering them susceptible to infections (e.g., EBV and a paramyxoviridae-like virus). Additionally, the concurrent presence of the autoimmune conditions, including autoimmune hemolytic anemia,[61] EBV,[43,44] and paramyxoviridae-like viruses,[43,45] have all been reported in PIGCH cases associated with CLL. However, PIGCH can also occur in patients with CLL in the absence of an autoimmunity disorder and viral infection.[60]

There are two possible mechanisms in the formation of giant hepatocytes: the failure of the cytoplasm to divide at the time of nuclear division and the fusion of individual cells to form a syncytium. As shown by an electron microscope study, in contrast to the normal-sized hepatocytes that have ultrastructural signs of necrosis, giant multinucleated hepatocytes from a PIGCH case due to clometacin administration did not show any ultrastructural abnormality. Instead, they had the appearance of active cells with abundant endoplasmic reticulum and numerous mitochondria, thus indicating that giant multinucleated hepatocytes were regenerative rather than degenerative cells, and the formation of giant multinucleated hepatocytes was due to nuclear division without cytoplasmic division.[50] However, in PIGCH associated with HCV, CLL,[37] and autoimmune hepatitis,[23] giant cells were strongly positive for keratin 8/18 (mature hepatocyte marker) and cyclin D1 (G1 phase marker),[37] and negative for Ki-67 (proliferation marker) and keratin 19/keratin 7 (intermediate hepatocyte makers),[23] hence indicating that nuclear division was a less likely explanation for the giant cell formation. On the other hand, the identification of intracellular plasma membrane remnants in the giant multinucleated hepatocytes indicated that the fusion of hepatocytes was a more likely mechanism for giant cell formation.[10] Therefore, further studies would be needed to clarify the exact mechanism of the giant cell formation.

There is still no consensus on the management of PIGCH. The treatment is typically dictated by the underlying condition. For cases associated with autoimmune etiology, treatment is usually composed of corticosteroids and immunosuppressants, such as azathioprine,[20–22,24,25,30] mycophenolate mofetil,[35,82] cyclosporine,[33] and cyclophosphamide.[11] Ursodeoxycholic acid has also been used either as a single agent or in combination with corticosteroids and other immunosuppressants as a therapy to reduce cholestasis.[7,10,24,31] Antiviral therapy is used in PIGCH cases associated with viral infections, e.g., acyclovir[43] or ribavirin[63] for paramyxoviral-related infections, interferon and ribavirin for HCV infections,[16,39] ganciclovir for HHV-6,[40] highly active antiretroviral therapy (HAART) for HIV infections,[28] and penicillin for syphilis infections.[52] In cases related to CLL, treatment usually includes a

Table 1. Comparison of the deceased versus living PIGCH patients in the clinical, laboratory, and histological parameters

	Deceased (n = 17)	**Living (n = 51)**	***p***
Age (n = 68)	60.0 (25–76)	39.0 (18–79)	0.067
Gender (n = 68)			0.779
male	9 (52.9%)	30 (58.8%)	
female	8 (47.1%)	21 (41.2%)	
Region (n = 68)			0.568
America	4 (23.5%)	19 (37.3%)	
Europe	9 (52.9%)	21 (41.2%)	
Asia	4 (23.5%)	11 (21.6%)	
Hg (g/dL) (n = 17)	11.1 (4.8–12)	11.8 (8.4–14)	0.209
WBC(x10^9/L) (n = 20)	9.8 (2.4–35)	12.8 (2.61–237.8)	0.135
Plt (x10^9/L) (n = 20)	126.0 (73–200)	207.0 (75–611)	0.040
IgG (g/L) (n = 30)	26.9 (17.6–38.76)	23.2 (4.93–47.1)	0.543
Elevated IgG	7 (100.0%)	16 (69.6%)	0.154
AST (U/L) (n = 61)	406.0 (56–2,385)	529.0 (40–5,350)	0.551
ALT (U/L) (n = 66)	216.0 (39–5,609)	469.0 (55–4,670)	0.934
ALP (U/L) (n = 49)	266.0 (47–727)	231.0 (57–828)	0.795
GGT (U/L) (n = 29)	159.5 (10–320)	190.0 (22–1,500)	0.218
TB (mg/dl) (n = 56)	18.0 (1–42)	8.4 (0.7–33.6)	0.022
Elevated TB	14 (93.3%)	37 (90.2%)	>0.9999
DB (mg/dl) (n = 26)	13.5 (1.92–34.4)	9.0 (2–21.4)	0.430
Elevated DB	11 (100.0%)	15 (100.0%)	>0.9999
INR (n = 19)	1.6 (1.1–2.32)	1.5 (0.9–6.2)	0.668
Albumin (g/dL) (n = 25)	2.7 (2.2–3.3)	3.1 (2.4–4.1)	0.012
Total protein (g/dL) (n = 16)	5.6 (4.5–7)	6.8 (5.4–10)	0.056
Positive ANA (n = 55)	8/14 (57.1%)	25/41 (61.0%)	0.758
Positive SMA (n = 44)	5/10 (50.0%)	12/34 (35.3%)	0.473
Positive AMA (n = 39)	2/11 (18.2%)	6/28 (21.4%)	>0.9999
Etiology (n = 68)			0.923
Autoimmune	5 (29.4%)	17 (33.3%)	
Viral	5 (29.4%)	9 (17.6%)	
Medication	1 (5.9%)	6 (11.8%)	
Malignancy	1 (5.9%)	4 (7.8%)	
Combined etiologies	4 (23.5%)	12 (23.5%)	
Others	1 (5.9%)	3 (5.9%)	
Histology			
Interface hepatitis (n = 24)	6/6 (100.0%)	15/18 (83.3%)	0.546
Necrosis (n = 39)	11/11 (100.0%)	26/28 (92.9%)	>0.9999
Lobular inflammation(n = 20)	5/5 (100.0%)	14/15 (93.3%)	>0.9999
Portal inflammation (n = 34)	10/10 (100.0%)	24/24 (100.0%)	>0.9999
Cholestasis (n = 27)	10/11 (90.9%)	14/16 (87.5%)	>0.9999
Steatosis (n = 9)	2/3 (66.7%)	3/6 (50.0%)	>0.9999
Fibrosis (n = 51)	13/15 (86.7%)	31/36 (86.1%)	>0.9999
Cirrhosis (n = 51)	4/15 (26.7%)	7/36 (19.4%)	0.711
Distribution of giant cells (n = 27)			0.017
Diffuse	4/5 (80.0%)	4/22 (18.2%)	

The data are presented as a median (range) or number (%). Hg, hemoglobin; WBC, white blood cells; Plt, platelet; IgG, immunoglobulin G; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; TB, total bilirubin; DB: direct bilirubin; INR, international normalized ratio; ANA, antinuclear antibodies; SMA, smooth muscle antibody; AMA, antimitochondrial antibody.

combination of immunosuppression (e.g., corticosteroids, cyclophosphamide, and azathioprine) and CLL directed therapy (anti-CD20 antibody, chemotherapy and/or ibrutinib).[59–61] For patients with rapid progression and a fatal process, liver transplantation is the last resort.

Our analysis was the first to comprehensively characterize the clinical, laboratory, and histological features associated with the outcome of PIGCH. In contrast to previous studies indicating that the prognosis of PIGCH was dictated by the underlying etiology,[22,47] we did not find any differences between the etiological composition between the patients with a poor or good outcome. Instead, the patients with a poor outcome were characterized by older age, lower levels of platelets and albumin, higher level of total bilirubin, and diffuse distribution pattern of giant cells in the liver.

Nevertheless, there are still unanswered questions about PIGCH. One enigmatic issue is the recurrence after liver transplantation. In cases of rapid progression to liver failure, liver transplantation was used as a rescue treatment. However, the transplant was still burdened by the risk of the recurrence of disease. The recurrence of giant cell hepatitis after one[63] or two liver transplantations[83] were documented. In some patients, no etiology could be identified.[83–85] Interestingly, Shah *et al*. reported a patient receiving a liver transplantation for giant cell hepatitis at the age of 10 months. Following the transplantation, the patient did well on a maintenance regimen of prednisone, azathioprine, and cyclosporine until aged 18 years when the patient developed recurrent giant cell hepatitis that was then successfully treated with ribavirin.[86] It was hypothesized that the recurrence of the disease after transplantation was due to a viral etiology located in the extrahepatic sites.[63] Ribavirin has since demonstrated to be successful in treating recurrent diseases leading to normalization of the liver enzyme,[86] reduced inflammation and number of giant cells,[84] and even normalized liver histology[63] in some cases. Nonetheless, this regimen was not always successful.[83] Next-generation sequencing (NGS) based metagenomics has been successfully used to detect novel and rare infections[87] and may open a new chapter in identifying viral etiologies associated with PIGCH.

The limitations of our meta-analysis included the quality of the case report and possible publication bias. For example, the detailed histological description was not always provided in the case reports. The distribution pattern of giant cells was mentioned in only 27 patients. Moreover, only 36 patients had follow-up data. Regarding publication bias, the cases of PIGCH without a clear etiology identified might be underestimated due to the fact that cases without a clear etiology might not have been reported in the publication. Thus, caution should be used when interpreting and applying the related findings.

Conclusions

PIGCH is a rare, heterogenous disease entity with a variable clinical course and prognosis. Poor outcome was associated with old age, low levels of platelets and albumin, high level of total bilirubin, and diffuse distribution pattern of giant cells in the liver. Further studies would be needed to better understand the disease mechanisms and unmask any additional etiological factors and targeted therapies.

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Conflict of interest

Zhang X has been an editorial board member of the *Journal of Clinical and Translational Pathology* since May 2021.The authors have no other conflicts of interest to disclose.

Author contributions

Jiao J reviewed the literature and drafted the manuscript; Zhang X provided the overall intellectual input, reviewed the literature, and edited the manuscript; all authors approved the final version to be published.

Data sharing statement

The data used to support the findings of this study are included within the article.

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