

World Journal of *Gastroenterology*

World J Gastroenterol 2024 April 14; 30(14): 1934-2067



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- 1941 Immune checkpoint inhibitor-associated gastritis: Patterns and management
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- 1949 Liver biopsy in the post-hepatitis C virus era in Japan
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Tang JX, Zhao D
- 1963 Bowel function and inflammation: Is motility the other side of the coin?
Panarese A

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- 1968 Necroptosis contributes to non-alcoholic fatty liver disease pathoetiology with promising diagnostic and therapeutic functions
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- 1982 Omics-based biomarkers as useful tools in metabolic dysfunction-associated steatotic liver disease clinical practice: How far are we?
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ORIGINAL ARTICLE**Retrospective Study**

- 1990 Characteristics of early gastric tumors with different differentiation and predictors of long-term outcomes after endoscopic submucosal dissection
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Observational Study

- 2006 Preoperative albumin-bilirubin score and liver resection percentage determine postoperative liver regeneration after partial hepatectomy
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- 2018** *Fusobacterium nucleatum*-induced imbalance in microbiome-derived butyric acid levels promotes the occurrence and development of colorectal cancer
Wu QL, Fang XT, Wan XX, Ding QY, Zhang YJ, Ji L, Lou YL, Li X
- 2038** Comparative transcriptomic analysis reveals the molecular changes of acute pancreatitis in experimental models
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The WJG is now abstracted and indexed in Science Citation Index Expanded (SCIE), MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 edition of Journal Citation Reports® cites the 2022 impact factor (IF) for WJG as 4.3; Quartile category: Q2. The WJG's CiteScore for 2021 is 8.3.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*, Production Department Director: *Xiang Li*, Cover Editor: *Jia-Ru Fan*.

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

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PUBLICATION DATE

April 14, 2024

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Shanghai Pancreatic Cancer Institute and Pancreatic Cancer Institute, Fudan University
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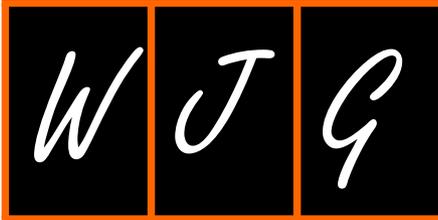
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Liver biopsy in the post-hepatitis C virus era in Japan

Yoshihiro Ikura, Takako Okubo, Yasuhiro Sakai

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Jiang X, China; Jiang W, China

Received: December 26, 2023

Peer-review started: December 26, 2023

First decision: January 24, 2024

Revised: February 5, 2024

Accepted: March 25, 2024

Article in press: March 25, 2024

Published online: April 14, 2024



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Abstract

In Japan, liver biopsies were previously crucial in evaluating the severity of hepatitis caused by the hepatitis C virus (HCV) and diagnosing HCV-related hepatocellular carcinoma (HCC). However, due to the development of effective antiviral treatments and advanced imaging, the necessity for biopsies has significantly decreased. This change has resulted in fewer chances for diagnosing liver disease, causing many general pathologists to feel less confident in making liver biopsy diagnoses. This article provides a comprehensive overview of the challenges and potential solutions related to liver biopsies in Japan. First, it highlights the importance of considering steatotic liver diseases as independent conditions that can coexist with other liver diseases due to their increasing prevalence. Second, it emphasizes the need to avoid hasty assumptions of HCC in nodular lesions, because clinically diagnosable HCCs are not targets for biopsy. Third, the importance of diagnosing hepatic immune-related adverse events caused by immune checkpoint inhibitors is increasing due to the anticipated widespread use of these drugs. In conclusion, pathologists should be attuned to the changing landscape of liver diseases and approach liver biopsies with care and attention to detail.

Key Words: Liver biopsy; Alteration; Post-hepatitis C virus era; Steatotic liver disease; Hepatic tumors; Immune checkpoint inhibitors

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Core Tip: Over the past 30 years in Japan, liver biopsies for assessing hepatitis C virus (HCV) hepatitis and HCV-related liver cancer were common but declined due to advanced treatments and imaging. This shift decreased diagnostic opportunities and eroded general pathologists' confidence in conducting liver biopsies. This editorial outlines key challenges: Understanding steatotic liver diseases as independent conditions, caution in diagnosing nodular lesions to prevent misinterpretation, and addressing hepatic injuries caused by immune checkpoint inhibitors. It stresses the need for pathologists to adapt to evolving liver disease landscapes and approach biopsies meticulously.

Citation: Ikura Y, Okubo T, Sakai Y. Liver biopsy in the post-hepatitis C virus era in Japan. *World J Gastroenterol* 2024; 30(14): 1949-1957

URL: <https://www.wjgnet.com/1007-9327/full/v30/i14/1949.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v30.i14.1949>

INTRODUCTION

I (Yoshihiro Ikura) started my career in pathology in Japan about 30 years ago, when abundant liver biopsies for interferon treatment for hepatitis C virus (HCV)[1,2] were submitted to pathology laboratories, day after day (Figure 1). Those who do not know about those days may think that it must have been very tough, but it was rather easy because all we had to do was to evaluate the severity of hepatitis and diagnose hepatocellular carcinoma (HCC).

In 2014, oral direct-acting antiviral agents (DAAs) were introduced[3,4], resulting in a steady decline of liver biopsies in Japan (Figure 2). Pretherapeutic histologic examination is not required for DAA administration[5], and most HCC cases can be treated based solely on radiological findings[6]. Consequently, the necessity of pathologic assessment of liver specimens is decreasing. This is a favorable change for minimizing patients' burden. However, opportunities for general pathologists to learn hepatic histopathology have decreased.

The changing landscape of liver diseases in Japan has caused many general pathologists to lack confidence in making liver biopsy diagnoses. This article categorizes the current issues surrounding liver biopsies in Japan and provides an overview of how to address them.

DIFFERENTIAL DIAGNOSIS CENTERED AROUND STEATOTIC LIVER DISEASES

Liver biopsies from patients with steatotic liver diseases (SLDs; either metabolic dysfunction-associated or alcoholic) and positive for autoantibodies are frequently submitted to our pathology laboratory as consultation cases. Figure 3A and B shows an example of such a case, where steatosis and inflammatory injury are evident, but the portal area remains almost unaffected (Figure 3A). I informed the physician that the patient had steatohepatitis, which is characterized by hepatocyte ballooning and lipogranulomas (Figure 3B), there being no findings of autoimmune hepatitis (AIH).

Figure 3C-E provides a contrasting example. The liver biopsy of a diabetic patient shows inflammatory changes associated with steatosis, similar to the previous case (Figure 3C). Additionally, the portal area exhibits inflammation and fibrosis, and most importantly, inflammatory bile duct damage (Figure 3D) with a small granuloma formation (Figure 3E). These findings are typical of primary biliary cholangitis. The patient's serological test confirmed a positivity for anti-mitochondrial antibodies. Complications of SLDs are apt to obscure the features of autoimmune liver diseases.

Currently, SLDs are estimated to affect 30% of the general adult population[7]. It should be noted that 30% of patients with autoimmune liver diseases, as well as those who are positive for autoantibodies but do not have autoimmune liver diseases, also have SLDs (Figure 4). Pathology reports should provide comments on whether SLDs are complicated by other liver diseases, rather than differentiating between them.

Figure 5 shows results of the comparative biopsy findings before and after HCV eradication with DAAs[8]. While inflammation, fibrosis and iron deposition have improved, steatosis appears to have worsened. This indicates that steatosis was an independent lesion, and not connected to HCV hepatitis. The data suggest that it is time to completely revise the conventional perspective of steatosis as a secondary change linked to various liver diseases.

DIAGNOSIS OF NODULAR LESIONS

The diagnosis of classical HCV-associated HCC was relatively easy because almost all cases had cirrhosis in the background and were observed as clearly demarcated atypical hepatocyte proliferation bordered by fibrous bundles (Figure 6). The histologic features of the current HCCs differ significantly from those of the classic HCCs. HCCs are increasingly developing in livers with only mild steatosis, without hepatitis or cirrhosis. Pathologists in Japan must abandon their previous understanding that HCC is usually associated with cirrhosis[9,10]. Diagnosing HCC has become increasingly challenging. Immunostaining, such as Glypican-3 and CD34, is recommended for cases where morphological diagnosis is difficult.

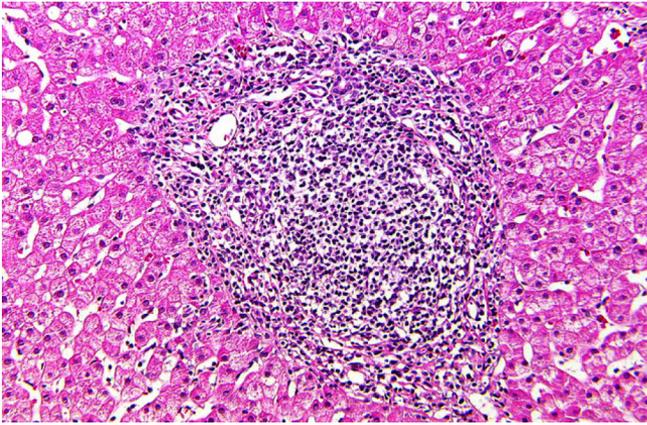


Figure 1 A typical histologic finding of chronic hepatitis C. A dense, follicle-like accumulation of lymphocytes is seen in the portal area. Hematoxylin-eosin, original magnification 200 ×.

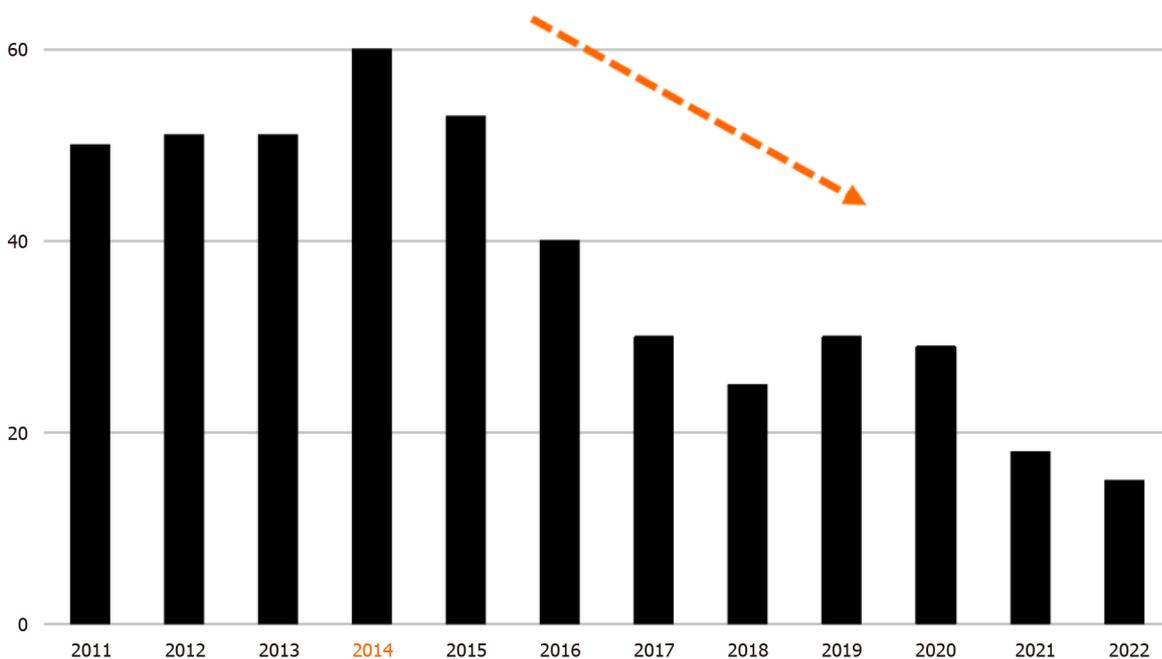


Figure 2 The number of liver biopsies conducted at Takatsuki General Hospital starting from 2011. In 2014, oral direct-acting antiviral agents were introduced, resulting in a steady decline of liver biopsies.

Among the biopsies for nodular lesions, the number of biopsies to diagnose HCC is decreasing. In addition to a certain percentage of tumor-free specimens, it is noteworthy that metastases and benign lesions have increased in recent years (Figure 7). Figure 8A-C shows a liver biopsy sent to our pathology laboratory as a consultation case, which originally had been diagnosed as HCC by biopsy a few years previously, then the tumor recurred repeatedly. The physician performed re-biopsy because of its unusual biological behavior inconsistent with HCC. No background cirrhosis was observed. The lesion consisted of cells with mild atypia and pale cytoplasm showing a cord-like arrangement. I couldn't accept the diagnosis of recurrent HCC, so I ordered immunostaining, which was positive for synaptophysin, and replied that it was probably a metastasis of a neuroendocrine tumor.

HEPATIC INJURY CAUSED BY DRUGS (INCLUDING IMMUNE CHECKPOINT INHIBITORS)

Drug-induced liver injury (DILI), including immune checkpoint inhibitors-related adverse effects (irAE), will become an increasingly important problem, and may require more detailed histologic assessment[11,12].

Figure 8D and E shows a liver biopsy from a patient clinically suspected of AIH, due to positive antinuclear antibody and abnormally elevated serum IgG. The liver tissue shows mild fibrosis, and the main site of injury being centrolobular, indicating acute injury. There are no findings such as hepatocyte rosettes or cobblestone-like arrangement that strongly suggest AIH. I recommended that the possibility of drug-induced injury should be considered first in terms of frequency.

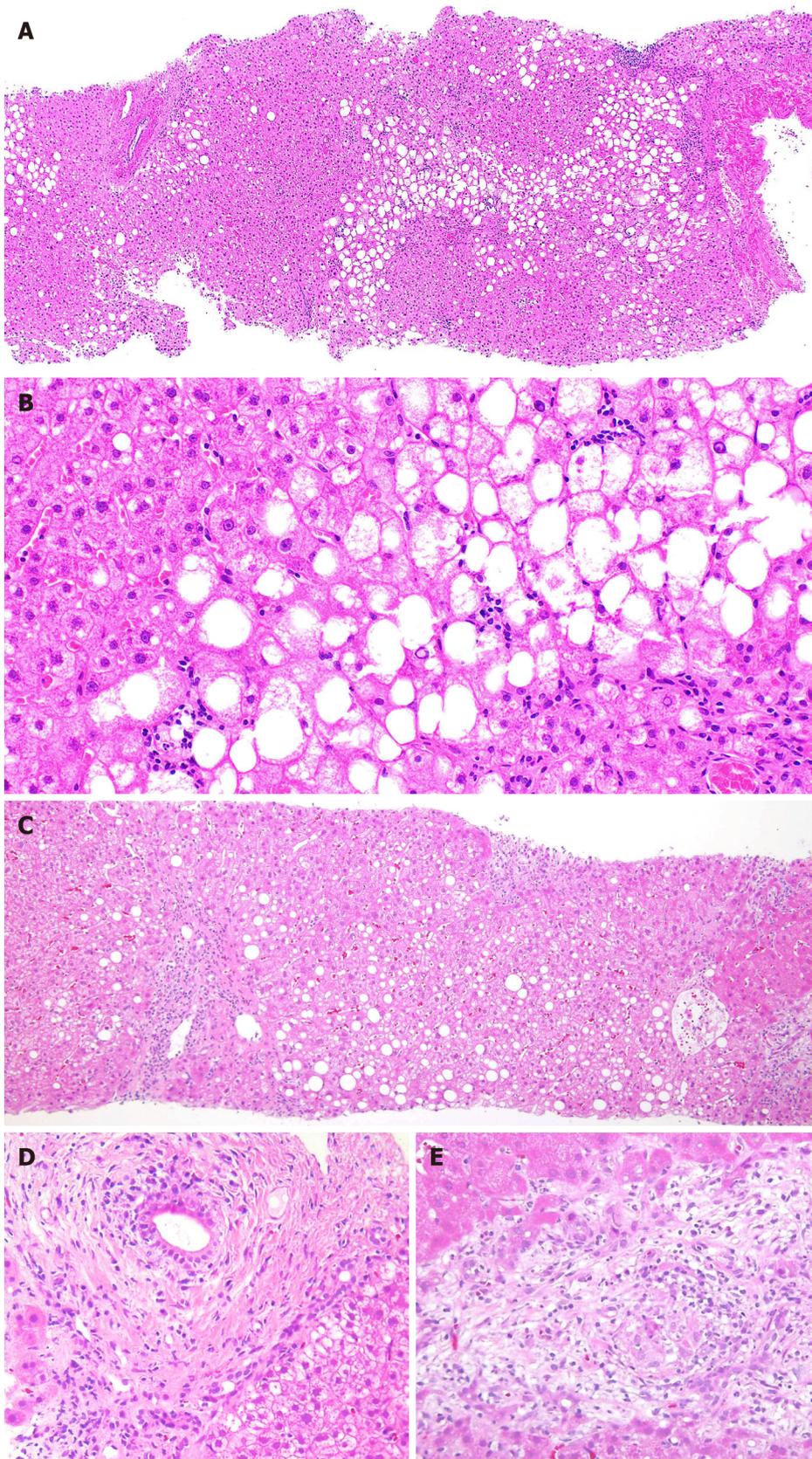


Figure 3 Biopsy from 2 patients. A and B: A liver biopsy from a 78-year-old male positive for antinuclear antibody. Hematoxylin-eosin (HE), original magnifications 40 × (A); HE, original magnifications 400 × (B); C-E: A liver biopsy from a 62-year-old male patient with diabetes mellitus. HE, original magnifications 100 × (C), 200 ×(D) and 200 ×(E).

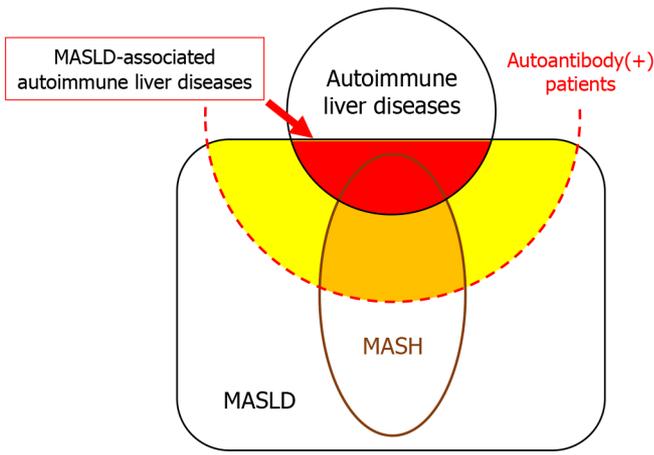


Figure 4 A schematic illustration indicating the relationships among metabolic-dysfunction associated steatotic liver disease, autoimmune liver diseases and autoantibody-positivity. MASLD: Metabolic-dysfunction associated steatotic liver disease; MASH: Metabolic-dysfunction associated steatohepatitis.

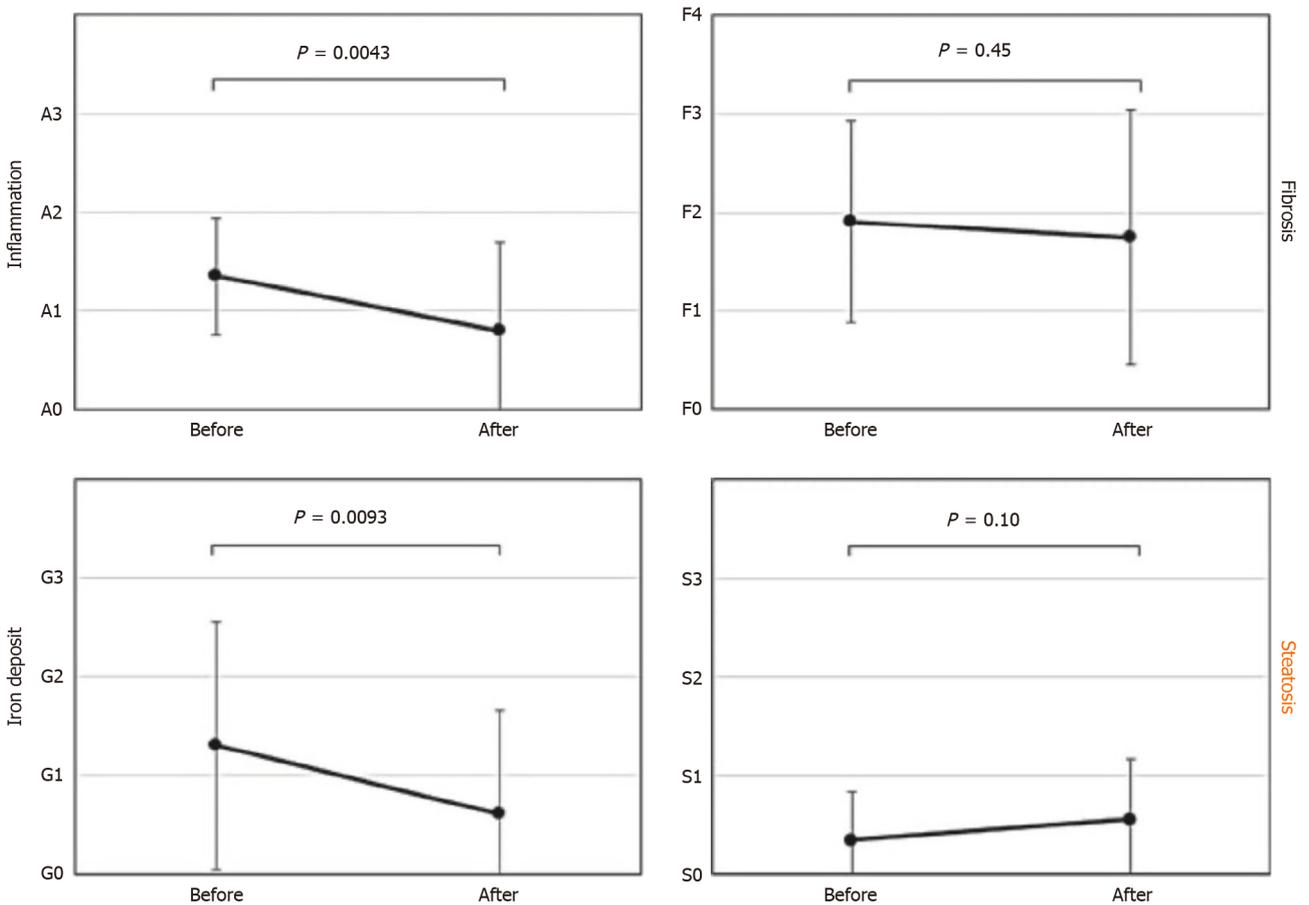


Figure 5 Findings of comparative biopsies before and after hepatitis C virus eradication with direct-acting antiviral agents. While inflammation, fibrosis and iron deposition have improved, steatosis has not changed and appears to have worsened[8].

The patient was later diagnosed with DILI, caused by one of the regular medications.

Figure 8F-I illustrates a case of bile duct injury that occurred three months after the initiation of nivolumab treatment for melanoma. Inflammatory cell infiltration and concentric fibrosis surround the interlobular bile ducts. The infiltrating cells were mostly CD3-positive T lymphocytes, with CD8-positive cells predominating over CD4-positive cells. CK7 staining clearly showed bile duct injury, which was ambiguous in the Hematoxylin & eosin slide. These pathologic changes were consistent with irAEs. After withdrawal of nivolumab, laboratory values returned to normal without the use of steroids.

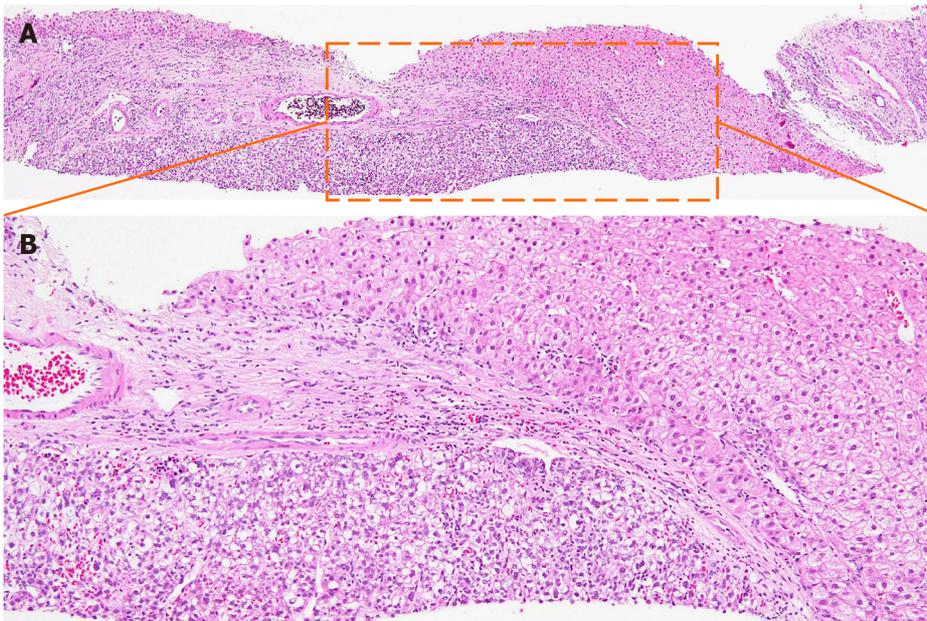


Figure 6 A typical case of hepatitis C virus-associated hepatocellular carcinoma. A: Hematoxylin-eosin (HE), original magnifications 20 ×; B: HE, original magnifications 100 ×.

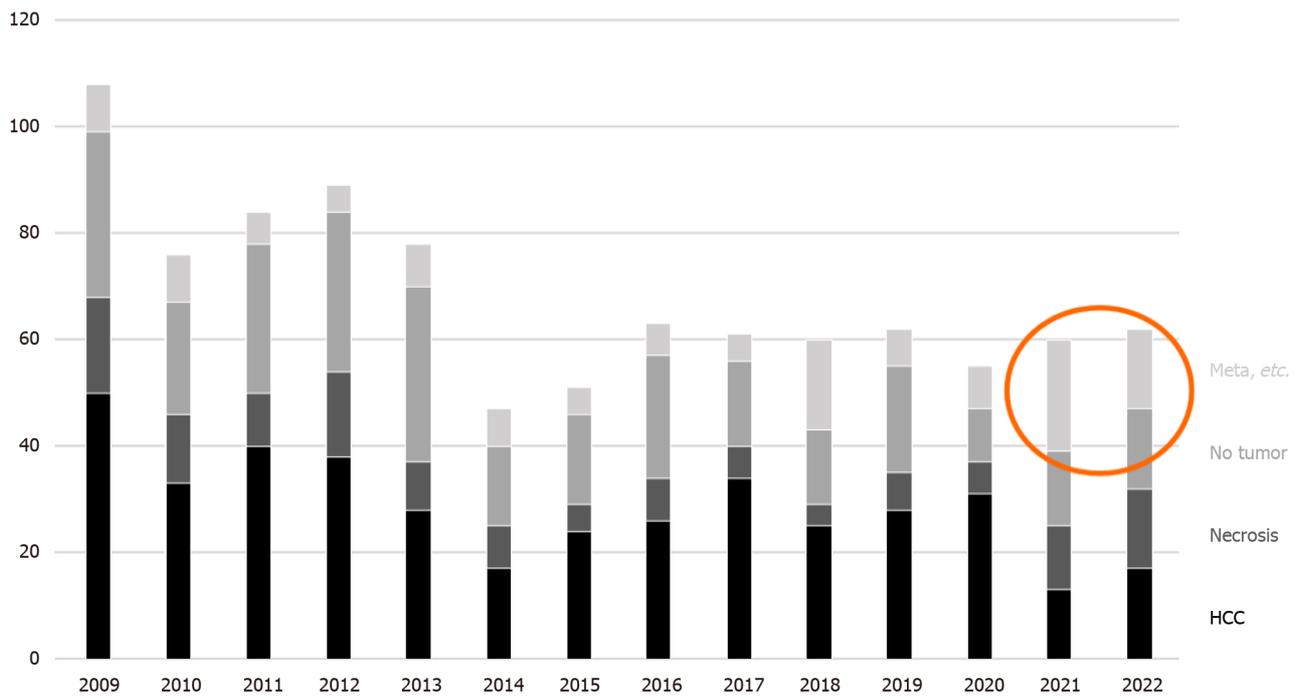
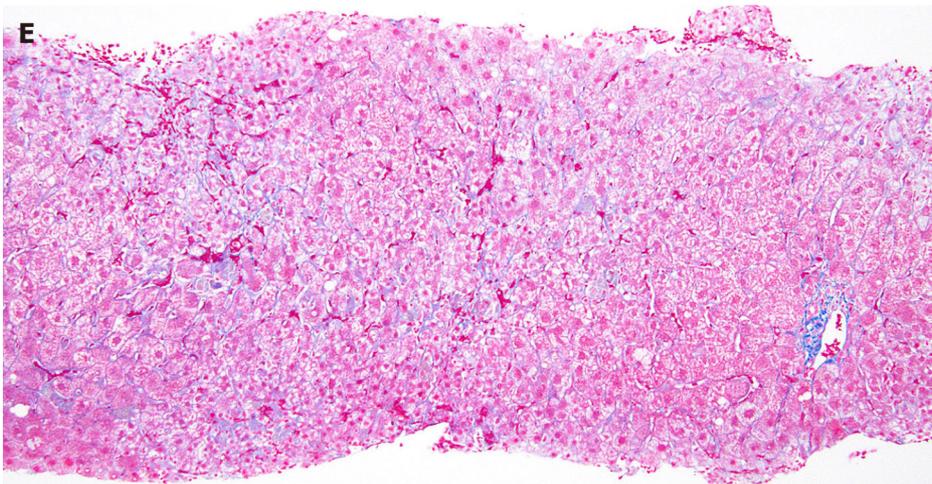
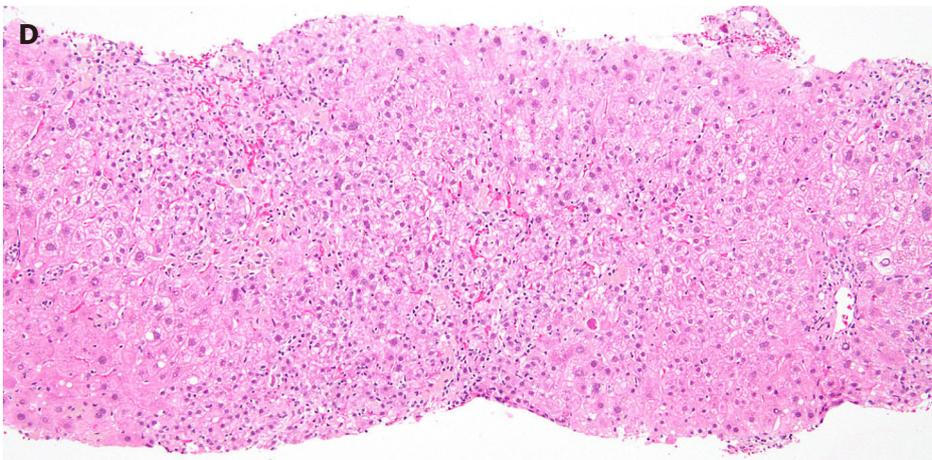
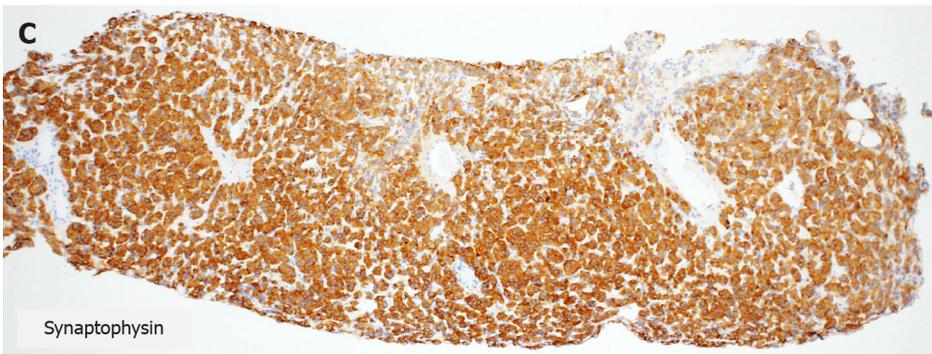
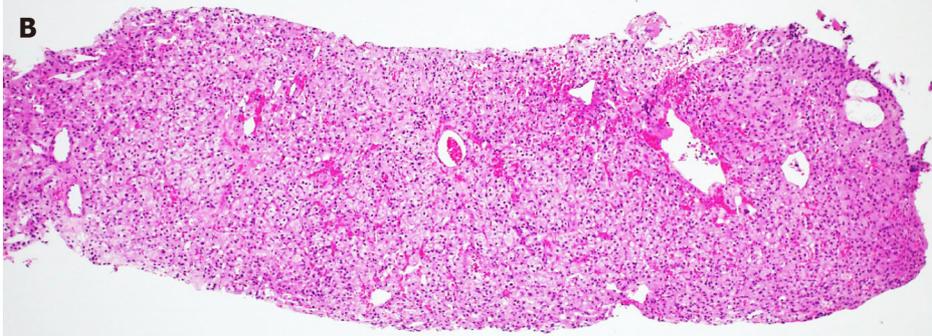
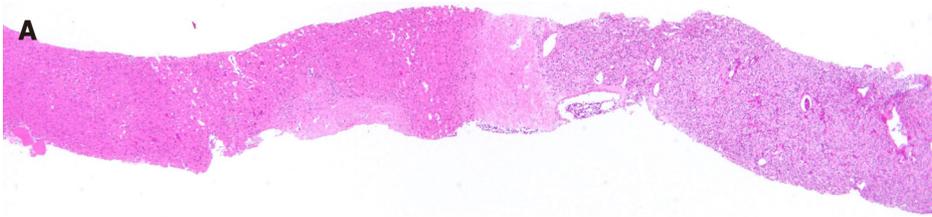


Figure 7 Trends in the number of tumor biopsies at Kansai Medical University Medical Center. Meta: Metastatic tumor; HCC: Hepatocellular carcinoma.

The histologic diagnosis of a liver biopsy requires careful evaluation, taking into account a detailed history of drug use.

CONCLUSION

In the post-HCV era, the number of liver biopsies is decreasing, but their variation is increasing. Pathologic diagnosis of liver biopsies needs appreciation of the changing landscape of liver disease.



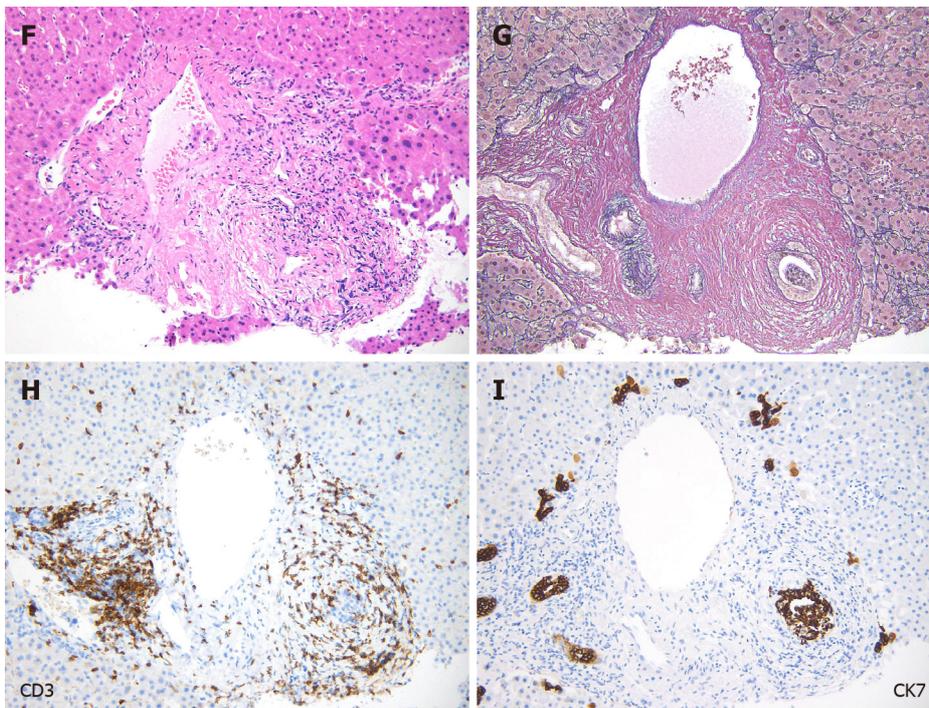


Figure 8 Liver biopsy from 3 patients. A-C: A biopsy of hepatic tumor from a 60-year-old female patient previously diagnosed as hepatocellular carcinoma. Hematoxylin-eosin (HE), original magnifications 20 × (A), 100 × (B); Immunostaining for synaptophysin, original magnification 100 × (C); D and E: A liver biopsy from a 72-year-old female patient diagnosed as drug-induced liver injury. HE, original magnification 100 × (D); Azan-Mallory stain, original magnification 100 × (E); F-I: A liver biopsy from a 76-year-old male patient with bile duct injury due to inhibitors-related adverse effects. HE, original magnification 100 × (F); Elastica van Gieson, original magnification 100 × (G); Immunostaining for CD3 and cytokeratin 7, original magnification 100 × (H, I). CK7: Cytokeratin 7.

ACKNOWLEDGEMENTS

We thank Dr. Noriyo Yamashiki from Kansai Medical University for providing valuable comments on current clinical issues related to various liver diseases.

FOOTNOTES

Author contributions: Ikura Y contributed to the conception and drafting of the manuscript; Ikura Y, Okubo T, and Sakai Y contributed to critical revisions of the manuscript.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest related to this article.

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S-Editor: Li L

L-Editor: A

P-Editor: Yuan YY

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