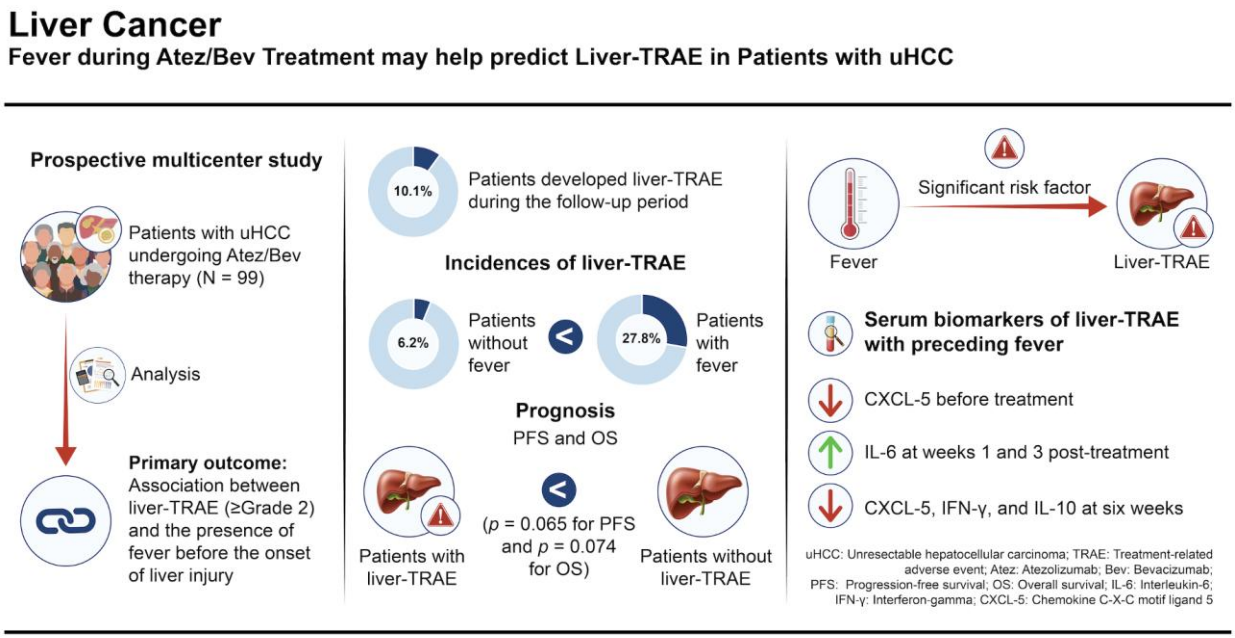
News Release

Early Signs of Liver Injury Induced by Immune Checkpoint Inhibitor in Patients with Unresectable Hepatocellular Carcinoma Identified!
–The Role of Fever and Humoral Factors as Predictive Markers of Adverse Events in Combination Therapy with Atezolizumab and Bevacizumab-



Ito T, et al. *Liver Cancer* 2025

Key Points

・ In patients with unresectable hepatocellular carcinoma (uHCC) who received atezolizumab plus bevacizumab (Atez/Bev) therapy, fever during treatment was significantly associated with the onset of treatment-related liver adverse events (liver-TRAEs) in a multicenter prospective observational study conducted at six institutions in Japan (n=99).

・ Patients who experienced fever had an approximately 4.5-fold higher incidence of CTCAE Grade 2 or higher liver-related adverse events (27.8% vs 6.2%) compared to those without fever. Fever was a significant independent risk factor (odds ratio 7.57, 95% confidence interval: 1.83–33.89, P=0.006).

・ In cases of liver injury accompanied by fever, distinct cytokine and chemokine changes were observed, including low pre-treatment levels of CXCL5, elevated levels of IL-6 at one and three weeks post-treatment, and decreased levels of CXCL5, IFN-γ, and IL-10 at six weeks.

・ Furthermore, pre-treatment MCP-1 (CCL2) was significantly correlated with both progression-free survival (PFS) and overall survival (OS), as a prognostic biomarker, suggesting its utility for prognostic stratification.

Summary
Severe cases of liver-TRAE are known to have a poor prognosis. We examined the association between fever induced by ICIs and subsequent liver injury, as fever is a reported prodromal symptom of irAEs. Our results revealed that patients who experienced ICI-induced fever had a significantly higher incidence of liver injury than those who did not. Additionally, patients who experienced fever showed changes in specific humoral factors, including IL-6, before or during Atez/Bev administration. These results suggest that fever during Atez/Bev treatment for uHCC may predict the risk of severe liver-TRAE, and that monitoring liver function and careful follow-up after fever onset are important. The results of this study were published in the online edition of the scientific journal Liver Cancer on June 14, 2025.

Research Background
HCC is one of the leading causes of cancer-related deaths in Japan. Systemic therapy for advanced, unresectable cases is an important treatment option that significantly impacts prognosis. In recent years, combination therapy using Atez, an ICI, and Bev, a monoclonal antibody that targets vascular endothelial growth factor (VEGF), has become the standard treatment for advanced HCC and has demonstrated promising antitumor effects. However, ICIs can cause immune-related adverse events (irAEs), which occur at a certain frequency and can lead to treatment discontinuation or worsen prognosis. Currently, there are no established indicators to predict which patients are prone to liver injury. Thus, there is an urgent need to identify clinically simple and early markers that can detect liver injury.

Research Results
This prospective observational study, centered on the Department of Gastroenterology at the University of Nagoya Hospital, involved six institutions and targeted 99 patients with unresectable advanced HCC from December 2020 to December 2023. The patients received Atez/Bev therapy, and the study analyzed the occurrence of fever during treatment, the subsequent development of liver injury, and changes in serum cytokine and chemokine levels before and after treatment.

The key findings are as follows:
<u>Association between fever and liver injury</u>
Of the 18 patients who developed a fever after treatment, five (27.8%) experienced Grade 2 or higher TRAEs, according to CTCAE Version 5. In contrast, the incidence of liver dysfunction was 6.2% (five cases) among the 81

patients who did not develop a fever.
Fever may be a significant risk factor for liver-TRAE (odds ratio: 7.57; P= 0.006).
Analysis of changes in blood cytokine and chemokine levels
In cases of liver-TRAE onset with fever, the following were observed:
・Pre-treatment CXCL5 levels were significantly lower.
・IL-6 levels increased at 1 and 3 weeks post-treatment.
・Significant decreases in CXCL5, IFN-γ, and IL-10 were observed at 6 weeks (all $P < 0.05$).
In the overall population, increases in IL-6 at one and three weeks and changes in IL-16, CXCL5, and CCL22 at six weeks were associated with liver-TRAE.
Identification of prognostic markers
Pre-treatment MCP-1 (CCL2) levels were significantly associated with progression-free survival (PFS) and overall survival (OS). Its usefulness as a predictor of treatment efficacy was confirmed (PFS: hazard ratio 1.008, OS: hazard ratio 1.013, P=0.02). However, MCP-1 was not associated with liver-TRAE.

Research Summary and Future Perspective
This multicenter, prospective study is the first to clarify, from clinical and molecular biological perspectives, the possibility that fever, an apparently minor symptom, may precede liver injury caused by ICIs. The dynamics of humoral factors, such as elevated IL-6 and decreased CXCL5, observed in the early stages of treatment suggest that these findings could contribute to a better understanding of the pathophysiology of immune-related liver injury. This could pave the way for personalized medicine.
Based on these findings, the following clinical applications are anticipated:
・Implementation of early liver function tests triggered by fever and rapid response to liver injury.
・Risk stratification of liver injury onset using cytokine profiles
・Development of safety monitoring guidance for ICI therapy based on fever and biomarkers.

Publication
Journal：Liver Cancer（Karger Publishers）
Authors: Takanori Ito[a*], Takafumi Yamamoto[a*], Kazuki Nishida[b], Yumiko Kobayashi[b], Kazuyuki Mizuno[a,c], Takaya Suzuki[a], Shinya Yokoyama[a], Kenta Yamamoto[a], Norihiro Imai[a], Yoji Ishizu[a], Takashi Honda[a], Masatoshi Ishigami[a], Toshinari Koya[d], Sayori Nakashima[e], Takehito Naito[f], Satoshi Yasuda[g], Teiji Kuzuya[h], Hidenori Toyoda[g], Yuichi Ando[c], Sachiyo Yoshio[i], Hiroki Kawashima[a]

Affiliation:
[a] Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine, Nagoya, Japan
[b] Division of Biostatistics, Department of Advanced Medicine, Nagoya University Hospital, Nagoya, Japan
[c] Department of Clinical Oncology and Chemotherapy, Nagoya University Hospital, Nagoya, Japan
[d] Department of Gastroenterology and Hepatology, Tosei General Hospital, Seto, Japan
[e] Department of Gastroenterology, Kariya Toyota General Hospital, Kariya, Japan
[f] Department of Gastroenterology, Toyohashi Municipal Hospital, Toyohashi, Japan
[g] Department of Gastroenterology and Hepatology, Ogaki Municipal Hospital, Ogaki, Japan
[h] Department of Gastroenterology and Hepatology, Fujita Health University School of Medicine, Toyoake, Aichi, Japan
[i] Department of Liver Diseases, The Research Center for Hepatitis and Immunology, National Center for Global Health and Medicine, Ichikawa, Japan

DOI: 10.1159/000546967

Japanese ver.
https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Liv_250619.pdf