Changing from NAFLD to MASLD: Similar Prognosis of Patients with HCC Under Atezo/Bev treatment between NAFLD and MASLD

Running title: Atezo/Bev for HCC: Changing from NAFLD to MASLD

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The consensus group composed of multiple societies has updated the terminology for nonalcoholic fatty liver disease (NAFLD) to refer to it as "metabolic dysfunction-associated steatotic liver disease" (MASLD) in order to more accurately reflect the underlying pathophysiology of the condition. The revision permitted us to discern the underlying factors of steatotic liver disease (SLD) with increased precision, while simultaneously eliminating the potential for stigmatization. Nonetheless, modifications to the terminology can sometimes result in misunderstandings, which may temporarily impede progress. In addition, to optimize the utilization of valuable research resources, it is imperative to build upon previous investigations on NAFLD and extend them to the study of MASLD. In this regard, several studies have already been conducted to accumulate evidence.

The etiology landscape of hepatocellular carcinoma (HCC) has undergone a significant transformation in the past decade owing to a marked decrease in active hepatitis C virus (HCV) infection, and the rising prevalence of NAFLD-related HCC has become a major public health issue worldwide. In contrast to HCV-related HCC, the incidence of NAFLD-related HCC is relatively low. However, due to the significant number of individuals affected by NAFLD, it poses a challenge from a cost-effective perspective to enclose and follow up all patients, resulting in detection in advanced stages. Recent breakthroughs in systemic therapy for advanced HCC, such as the use of molecular-targeted agents and immune checkpoint inhibitors (e.g., atezolizumab in combination with bevacizumab [Atezo/Bev]), have resulted in significantly improved prognoses for patients with these conditions. The impact of NAFLD on the prognosis of patients is a subject of ongoing discourse, as the efficacy of therapeutic interventions may be influenced by both favorable and unfavorable factors related to the underlying etiologies. Consequently, effective management and treatment of patients with HCC necessitates a profound comprehension of the prognostic implications of NAFLD in these patients. However, no studies have investigated the relationship between NAFLD and MASLD in individuals with advanced HCC who have undergone Atezo/Bev.
We aimed to compare the prognosis of unresectable HCC between patients with NAFLD and MASLD. This study included 216 consecutive patients with advanced HCC who received Atezo/Bev at 11 institutions in Japan between November 2020 and October 2023. All the patients were of Asian origin. The data of these participants were as follows: 78.7% male; median age 73 years; median body mass index 23.0 kg/m²; 98% performance status ≤1; 94% Child-Pugh class A; median alpha-fetoprotein 42.2 ng/mL (Table 1). SLD was diagnosed based on the presence of moderate or severe hepatic steatosis on ultrasonography. The most common line of chemotherapy was first-line (136/216, 63.0%), followed by second-line chemotherapy (64/216, 29.6%).

NAFLD was diagnosed in 17.6% (38/216) of the patients, including one patient who did not fulfill the cardiometabolic criteria for MASLD (Figure 1A). The present case was classified as cryptogenic SLD, and a significant proportion (97.4%) of the patients with NAFLD in our study were also diagnosed with MASLD. Thus, the backgrounds of the NAFLD and MASLD patients were nearly indistinguishable, a finding that is not surprising given that they differed by only one patient. (Table 1). Our findings align well with previous studies that reported that over 95% of NAFLD patients fulfilled the MASLD criteria.³,¹⁰ Figure 1B shows the Kaplan-Meier curve for overall survival. No significant difference was observed in the overall survival rate between the NAFLD and MASLD groups [median overall survival in patients with NAFLD and MASLD was 583 days (95% certificate index, 409–not applicable days) and 472 days (95% certificate index, 404–not applicable days), \( p = 0.877 \), respectively]. The rate of one-year/three-year survival were no significant difference between in patients with NAFLD and those with MASLD [one-year, 71.1% vs. 70.3%, \( p = 0.941 \); three-year, 26.3% vs. 24.3%, \( p = 0.843 \)] (Figure 1B).

In conclusion, these results indicate that the prognosis for patients with advanced HCC undergoing Atezo/Bev treatment with MASLD is comparable to that in patients with NAFLD. It is crucial to validate these findings through an international cohort comprised of a greater number
of patients.

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Authors' contributions
Hiroyuki Suzuki: study concept, design, and statistical analysis; Shigeo Shimose: data extraction, interpretation of data, and critical revision of the manuscript; Hideki Iwamoto: interpretation of data, drafting, and critical revision of the manuscript; Takashi Niizeki: interpretation of data and critical revision of the manuscript; Takumi Kawaguchi: interpretation of data and critical revision of the manuscript.

Conflict of interest:
References:


Figure Legends

Figure 1. Prognosis of HCC under Atezo/Bev combination therapy in the NAFLD and MASLD groups.

(A) The prevalence of NAFLD and MASLD in patients with HCC. (B) Probability of overall survival between the NAFLD and MASLD groups.

Abbreviations: HCC, hepatocellular carcinoma; Atezo/Bev, atezolizumab plus bevacizumab; NAFLD, nonalcoholic fatty liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; NA, not applicable; mOS, median overall survival.
Table 1. Baseline patients characteristics.

<table>
<thead>
<tr>
<th>Value</th>
<th>All (n = 216)</th>
<th>NAFLD (n = 38)</th>
<th>MASLD (n =37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>73</td>
<td>74.5</td>
<td>75</td>
</tr>
<tr>
<td>Sex, female/male</td>
<td>46/170</td>
<td>9/29</td>
<td>8/29</td>
</tr>
<tr>
<td>Etiology, NAFLD(MASLD)/HCV/HBV/Alcohol/Others</td>
<td>38/103/32/36/7</td>
<td>38/0/0/0/0</td>
<td>37/0/0/0/0</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.0</td>
<td>25.2</td>
<td>25.4</td>
</tr>
<tr>
<td>Performance status, 0/1/2</td>
<td>179/32/5</td>
<td>30/8/0</td>
<td>29/8/0</td>
</tr>
<tr>
<td>Child-Pugh class, A/B</td>
<td>203/13</td>
<td>35/3</td>
<td>34/3</td>
</tr>
<tr>
<td>Alpha-fetoprotein (ng/mL)</td>
<td>42.2</td>
<td>34.6</td>
<td>32.9</td>
</tr>
<tr>
<td>BCLC, A/B/C</td>
<td>2/106/108</td>
<td>1/20/17</td>
<td>1/20/16</td>
</tr>
</tbody>
</table>

Data are presented as medians.

Abbreviations: NAFLD, non-alcoholic fatty liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; HCV, hepatitis C virus; HBV, hepatitis B virus; BCLC, Barcelona Clinic Liver Cancer.