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Editorial

The emerging age-pattern changes of patients with hepatocellular carcinoma in Korea

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See Article on Page 120

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide and the second leading cause of cancer-related death in Korea.[1] Previous studies have reported that the incidence rate of HCC in Asia is more than 10-fold than that in Western countries.[2] The highest age-adjusted incidence rates (>13.7–17.8 per 100,000) are recorded in East Asia (Korea, China, Mongolia, and Vietnam) and sub-Saharan Africa in 2020, which accounts for approximately 80% of liver cancer worldwide.[2] Hepatitis B virus (HBV) is still the predominant etiology of HCC in Korea, China, and Taiwan, accounting for approximately 60–70% of HCCs.[3] The prevalence of chronic hepatitis B (CHB) ranged from 8% to 10% in the general population in the 1980s and early 1990s in Korea. However, owing to the universal vaccination program launched in 1983, the prevalence of CHB has significantly decreased. The Korea Advisory Committee on Immunization Practices also implemented the Hepatitis B Perinatal Transmission Prevention Program in July 2002. This program aimed to screen all pregnant women for CHB infection, provide prophylactic hepatitis B immunoglobulin to all infants born to hepatitis B surface antigen (HBsAg)-positive mothers, and vaccinate all infants against HBV. The HBsAg-positivity rates in the 10–18 years group markedly declined to 2.2% in 1998, 1.9% in 2001, 1.9% in 2007, and 0.3% in the Korea National Health and Nutrition Examination Survey 2016.[4] Moreover, the use of potent nucleos(t)ide analogs significantly reduced the development of cirrhosis, leading to improved overall survival of patients with CHB.[5] All of these effective strategies have changed the incidence patterns of HCC over time in Korea.

Chon et al.[6] reported trends in HCC incidence in South Korea over 10 years (2008–2018) from the Korean National Health Insurance Service database (127,426 individuals) and predicted the incidence for the year 2028. From 2008 to 2018, the number and age-standardized incidence rates (ASRs; from 21.9 to 14.3 per 100,000 person-years) of HCC significantly decreased, except in older adults. Among individuals aged ≥80 years, the ASR significantly increased by 0.96% per year and the crude incidence rate of HCC also increased. From 2008 to 2018, the ASRs for individuals aged ≥80 years increased from 70.0 to 160.2 per 100,000 person-years.

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Interestingly, Chon et al.[6] also reported that the proportion of nonalcoholic fatty liver disease (NAFLD)-related HCC steadily increased from 2008 to 2018 (average annual percentage change, 2.7%; $P<0.001$), with a rapid increase from 2011 to 2018 at an average of 5.6% per year. NAFLD-related hepatocarcinogenesis is indeed characterized by a long-lasting and insidious development.[7-9] Patients with NAFLD-related HCC were generally older than those with virus-related HCC.[10] HCC risk is higher individuals with obesity[11] and diabetes,[12] as these conditions are two major risk factors for NAFLD. The pathogenesis of HCC in NAFLD is also independent of cirrhosis, and HCC in NAFLD might arise in the absence of fibrosis and histologically detectable inflammation. Obesity and excessive adipose tissue contribute to a chronic general low-grade inflammatory response, called lipotoxicity, and play an important role in hepatocarcinogenesis.[13] The alteration of gut microbiota in patients with NAFLD also leads to hepatocarcinogenesis,[14] which is affected by aging. Since Korea is a rapidly aging society, these factors might consistently increase the proportions of NAFLD-related HCC and older HCC patients.

The definition of "elderly" has become more difficult to agree. Generally, a chronological age of 65 years has been accepted as a threshold to define an "elderly" individual. In the scientific literature on HCC, the most commonly used threshold is 70 years.[15] More recently, clinical studies adopting thresholds of 75 or 80 years have been published.[16] The increasing age of patients with HCC brings some drawbacks to choosing treatment modality due to the occurrence of comorbidities, which can be associated with reduced tolerability and an increased risk of serious adverse events. The Eastern Cooperative Oncology Group performance status, which quantizes constitutional syndrome due to tumor burden, is one of the key factors that determine disease stage, consequently influencing the choice of treatment modality. Another problem frequently encountered in elderly patients with HCC is that they are relatively reluctant to undergo surgical resection or systemic therapies, erroneously considered too risky for older patients. Clinical trials specifically designed to compare HCC outcomes in older patients aged >75 years are lacking. IMbrave150 trial also included subjects with aged ≤71 years.[17] The available data on HCC outcomes in older patients with HCC are mainly from retrospective observational studies. Long-term survival in elderly patients with HCC is mainly dependent on their expected shorter life span than younger patients and the occurrence of comorbidities. Kim et al.[18] reported a retrospective Korean HCC cohort study showing that non-liver-related mortality was significantly higher in older patients (≥70 years) than in younger patients, although the overall survival was similar to that found in patients aged <70 years. Therefore, the allocation of treatment modalities should be determined according to HCC stage, liver function, and performance status,[19] rather than chronological age. Chronological age ≥75–80 years is not an absolute contraindication for surgical resection or systemic therapy. Older patients with resectable tumors and well-preserved liver function may benefit from surgical resection. Systemic therapy may also be a viable option for treating advanced HCC in older patients. Clinicians should carefully evaluate concomitant comorbidities, particularly cardiovascular diseases. Previous studies reported that tyrosine kinase inhibitors, including sorafenib and lenvatinib, were also effective and tolerable for older patients with HCC aged >70–75 years with more vigilant monitoring.[15,16] A recent multicenter analysis from Japan (n=317) also reported the safety and efficacy of atezolizumab plus bevacizumab in older patients with HCC aged ≥75 years. In a subgroup analysis of older patients aged 75–79, 80–84, and ≥85 years, w no significant differences were found in cumulative overall or progression-free survival and treatment-related adverse events among these age groups.[20] However, a recent multicenter retrospective observational study from Japan showed poorer tolerability to lenvatinib in older patients aged ≥80 years than in patients aged <80 years. Therefore, meticulous management[21] of adverse events is crucial for the adherence and maintenance of systemic therapies in older patients with HCC.

Changes in the epidemiology of chronic liver disease have led to changes in the age at HCC diagnosis in Korea. The proportion of older patients with HCC is gradually increasing. Additionally, Chon et al.[6] reported that by 2028, the number of patients with HCC aged ≥80 years will be greater than the number of HCC patients in 2008. It is not appropriate to re-

Abbreviations:

ASR, age-standardized incidence rate; CHB, chronic hepatitis B; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease

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strict the upper age limit for the HCC surveillance. Allocation of treatment modality should be determined according to HCC stage, liver function, and performance status, rather than chronological age.

Authors' contribution

Study conceptualization: YC and JWP; Drafting of the manuscript: YC; Critical revision of the manuscript: BHK, YC, and JWP

Conflicts of Interest

The authors have no conflicts to disclose.

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