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Effects of a DPP-4 Inhibitor and RAS Blockade on Clinical Outcomes of Patients with Diabetes and COVID-19 (*Diabetes Metab J* 2021;45:251-9)

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Studies have reported that people with chronic diseases such as diabetes mellitus (DM), obesity, and dyslipidemia have a higher risk of coronavirus disease 2019 (COVID-19) infection than does the general population and also have poor prognoses [1]. In terms of public health, establishing an effective, evidence-based treatment strategy for COVID-19 patients with chronic diseases is critical.

In this respect, our research has important implications for effective treatment and management of patients with DM that have confirmed COVID-19 infection [2]. This study was conducted using the national claims database of Korea published in May 2020, which was early in the COVID-19 epidemic . The research was conducted to answer some of the most important clinical questions about patients with DM who are infected with COVID-19. Our findings were released in preprint format on medRxiv.org prior to publication to facilitate early sharing and distribution to inform patient treatment and improve outcomes.

An important limitation of our study was the small number of subjects. The volume of COVID-19-related national databases open to general researchers in South Korea is limited. In fact, in our study, the total number of COVID-19 patients with DM identified in the National Health Insurance Review and Assessment Service (HIRA) database was 832. However, we conducted a careful analysis to overcome these limitations and found that the use of dipeptidyl peptidase-4 (DPP-4) inhibitors produces good clinical outcomes for Korean patients with DM who are infected with COVID-19.

In addition, unlike the preprint version, additional analysis was performed to improve the reliability of the study, which were included in the results we officially published in *Diabetes and Metabolism Journal*. This study used the National Health Insurance Service (NHIS) of Korea dataset, an independent claims database, in addition to the existing HIRA database [2]. The NHIS database operated independently of the HIRA database, and the data collected from the NHIS were additional to the claims data of subjects. Therefore, using both datasets, we were able to analyze additional clinical parameters such as national health check-up data [3]. Consequently, this analytical process allowed the research to address and overcome the limitations of our initial study.

Some recent reports have indicated conflicting information from the results of our study. In particular, in a study based on large claims data in the UK, the clinical course for patients that used DPP-4 inhibitors was negative [4]. However, other studies have shown similar results to our study. A study by Mirani et al. [5] found that the adjusted hazard ratio (HR) for mortality for DPP-4 inhibitors was 0.13. In the study by Solerte et al. [6], the HR for mortality of patients that used DPP-4 inhibitors was 0.44. In a meta-analysis, the odds ratio for mortality for patients that used DPP-4 inhibitors was 0.58 [7]. Because DPP-4 inhibition can contribute to modulation of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection pathway and cytokine storm, a potential clinical effect is pro-

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posed [8,9].

However, current studies have not provided definitive conclusions about the effectiveness of DPP-4 inhibitors in patients with DM with COVID-19. Because of the nature of the data structures in our study, only a short-term clinical course analysis was possible to determine important outcomes such as intensive care or death. Therefore, the results should be interpreted with these limitations in mind, and future studies should address this issue. It is important for clinicians and providers to monitor the clinical effects of recently released therapeutics for DM as the impact of these drugs might differ by ethnicity [10]. We do not fully understand the various pleiotropic effects of different antidiabetic drugs.

In addition, evidence-based research continues to accumulate on the treatment of COVID-19 patients with chronic diseases. Therefore, the results of this study should be considered when treating patients with COVID-19 and DM. Further, additional studies will provide insights to refine the best treatment options for patients with chronic illness and COVID-19 infections.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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