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In-hospital outcome in COVID-19 patients: Did we learn something?

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Coronavirus disease 2019 (COVID-19) has fundamentally changed everything since December 2019 when World Health Organization (WHO) confirmed this virus for the first time. A novel coronavirus, SARS-CoV-2, spread extremely fast around the globe and WHO claimed a global pandemic in March 2020.

One of the most important questions that was raised at the beginning of pandemic considered risk factors that are associated with SARS-CoV-2 infection, worse clinical manifestation of COVID-19 and adverse outcome. The first results indicated that advanced age, male sex, previous cardiovascular and respiratory diseases were risk factors for infection and worse clinical outcomes (treatment in intensive care units, intubation and in-hospital mortality) [1]. However, these studies were usually performed in one center, included limited number of patients of only one race, provided relatively short follow-up with scarce information about confounding factors that might interfere the final results [1]. Due to lack of data about potential confounding factors and misinterpretation of obtained results, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) were declared as potentially dangerous in COVID-19 patients [2], which raised many questions. Fortunately, large

data showed that ACEIs and ARBs were not associated with higher risk of infection, intubation or mortality in COVID-19 patients [3].

In this issue of the Journal, Terlecki et al. [4] reported data about the relationship between CV diseases, CV therapy and in-hospital mortality in the large cohort of COVID-19 patients from a single-center registry in Poland. The authors confirmed existing evidence that advanced age, male sex, diabetes mellitus, and pre-existing heart failure were the major predictors of adverse outcomes in these patients. The most innovative part of this investigation refers to the protective effect of CV medications, ACEI/ARB, beta-blockers, statins, and antiplatelet agents, in COVID-19 patients [4].

The most prevalent CV diseases in this study were arterial hypertension, hyperlipidemia, diabetes mellitus, coronary artery disease, heart failure, atrial fibrillation, and stroke [4]. Age over 65 years, male sex, pre-existing diabetes mellitus, and heart failure were independent predictors of in-hospital mortality, whereas treatment with ACEIs/ARBs, beta-blockers (BBs), statins, or antiplatelet therapy was related with lower in-hospital mortality [4]. Stroke also showed a borderline significance as an independent predictor of in-hospital mortality ($P = 0.07$).

The effect of ACEI/ARB on outcome in COVID-19 patients has not been completely understood because results still vary in different studies depending of which outcome has been investigated and which parameters were used for adjustment in statistical models [5]. In the large cohort of 824,650 patients with hypertension from a US integrated healthcare system was found that ACEI/ARB use did not increase the risk of COVID-19 infection [5]. Interestingly, ACEI use was associated with decreased risk of COVID-19 infection among hypertensive patients older than 85 years. Recently published meta-analysis revealed that use of ACEI/ARB was independently associated with the reduction of severe adverse events and mortality in all patients, as well as in subgroup of hypertensive patients [6]. Ren et al. [7] included 2,100,587 participants in a meta-analysis and revealed no association between prior usage of antihypertensive medications including ACEIs/ARBs, calcium channel blockers (CCBs), BBs, or diuretics and the risk and severity of COVID-19. Furthermore, the severity and mortality were significantly lower in hypertensive patients with prior usage of ACEIs/ARBs [7]. The beneficial effect of statins on mortality in COVID-19 has been also recently reported [8]. However, there are also large investigations that showed no evidence that antihypertensive therapy was associated with increased risk of COVID-19 infection or mortality [9]. ACEI/ARBs, CCBs and diuretics with lower risk of

COVID-19 infection, whereas only BBs were associated with higher risk of COVID-19 of infection [9]. Other investigation showed that BBs were independently associated with better outcome and less severe course of disease, whereas CCBs were related with poor outcome (ICU admission and mortality) [10]. ACEI/ARBs and diuretics were not associated with outcome [10].

The effect of antithrombotic therapy, both antiplatelet and anticoagulant, on outcome in COVID-19 has not been established yet. Russo et al. [11] recently reported that this therapy was not associated with better outcome in patients with severe form of COVID-19 with acute respiratory syndrome at presentation. Meta-analysis that included 5,970 COVID-19 patients confirmed that antiplatelet therapy did not decrease mortality in these patients [12]. On the other hand, the study that included almost 2,000 COVID-19 patients reported positive effect of aspirin on in-hospital mortality [13].

The major limitation of available studies is the lack of information about the control of primary disease (hypertension, heart failure, coronary artery disease, atrial fibrillation) and its control before and during COVID-19 infection. The recent study demonstrated that patients with stage 1 uncontrolled blood pressure (140/90–159/99 mm Hg) had lower risk of COVID-19 death compared with patients with well-controlled blood pressure, who were older, with more comorbidities, and had been diagnosed with hypertension for longer [14]. However, in the circumstances with similar age, prevalence of comorbidities and duration of hypertension, one would expect that control of main comorbidities in COVID-19 patients such as hypertension, heart failure, diabetes, atrial fibrillation or coronary artery disease have essential role in prediction of outcome in COVID-19 patients. In the current study Terlecki et al. [4] did not include other medications, such as diuretics, antidiabetics and anticoagulants, in the final multivariable analysis. Even though data about BMI and creatinine level were provided, the authors did not consider the effect of obesity or renal dysfunction on the outcome in this population. The same is with potential effect of pulmonary diseases (asthma and COPD) that was not examined in the statistical model. Data about specific or unspecific therapy used for treatment of COVID-19, aside of oxygen therapy, were not provided and it might be essential in prediction of adverse outcomes.

The diversity of published results about CV diseases and therapy on outcome in COVID-19 patients reveals the lack of understanding of mechanisms that would potentially explain the relationship (positive or negative) between CV drugs and

COVID-19. Furthermore, detailed analysis of all potential risk factors on severity and outcome of COVID-19 with adequate follow-up would be very much appreciated.

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