SARS-CoV-2 infection and diabetes mellitus: A North Eastern Romanian experience

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Abstract. As it spread globally, the new SARS-CoV-2 virus was first confirmed in Romania in February 2020, inevitably infecting individuals with diabetes mellitus (DM) along the way. Diabetes is known to affect the response of the body to pathogens and, according to studies conducted in the last 3 months, it appears that diabetic patients are at a higher risk for developing severe forms of the disease and multiple complications. We performed a retrospective study in order to assess the patients with SARS-CoV-2 infection and DM admitted to 'Sf. Parascheva' Clinical Hospital of Infectious Diseases from March 4th until June 30th, 2020. Of the total 1,080 patients admitted during this period, 85 patients (7.87%) had underlying DM, mostly type 2 (82 cases, 96.46%); the mean age of these patients was 62, and 42 were men (49.41%). Chest CTs revealed indicative SARS-CoV-2 images for all patients and their treatment included individually tailored administration of hydroxychloroquine/lopinavir + ritonavir/enoxaparin sodium/tocilizumab/antibiotherapy according to the then national and international guidelines. In total, 70 patients (82.35%) were cured and 15 succumbed to MODS and/or associated neoplasia, bringing the fatality rate to 17.64%. Although advanced age and DM have been associated with aggravated forms of SARS-CoV-2 infection, over 80% of the patients included in the present study were cured. Nonetheless, diabetes appears to be a significant predictor of morbidity and mortality in the SARS-CoV-2 infection.

Introduction

In December 2019, a new strain of virus causing severe acute respiratory syndrome (SARS-CoV-2) appeared for the first time in the city of Wuhan, Hubei province, China. The virus spread rapidly and, at the time of writing this study, more than 10 million cases were reported in 216 countries (1).

Coronaviruses (CoV), generally known to cause acute respiratory infections, are enveloped viruses that have a single-stranded, positive-sense RNA genome (2). Although the majority of coronavirus infections affecting humans are mild, there have already been two important outbreaks of two types of coronaviruses causing multiple severe pneumonias: The severe acute respiratory syndrome coronavirus (SARS-CoV), with a mortality rate of up to 10%, and Middle East respiratory syndrome coronavirus (MERS-CoV), with a mortality rate of over 34% (3,4). Although SARS-CoV-2 has exhibited similar phylogenetic and clinical features with SARS-CoV, this new coronavirus appears to be considerably more easily transmissible, albeit less deadly (5). Typical symptoms, encountered in over 40% of the cases include fever, cough, fatigue and shortness of breath, and also less frequent common symptoms including anosmia and ageusia (6).

As the SARS-CoV-2 pandemic unfolded, diabetes mellitus (DM) was already one of the leading causes of morbidity and mortality throughout the world, and it is known that DM produces a plethora of macrovascular and microvascular complications that ultimately impact overall patient survival (7). In this new context, several studies reported apparent associations between diabetes mellitus, acute respiratory distress syndrome, more severe disease, and increased mortality (8-11). Multiple explanations have been put forth for this hypothesized association between DM as the underlying disease and the increased severity of SARS CoV-2 infection. Natural immunity, which is the primary line of defense against SARS-CoV-2, is inevitably weakened in patients that have uncontrolled DM; consequently, the virus proliferates unrestricted within the host (12). In fact, it has been demonstrated that even short-term hyperglycemia can briefly paralyze the natural immune system (13). In addition, DM promotes an increased pro-inflammatory cytokine response, mainly involving interleukin (IL)-1, IL-6 and tumor-necrosis factor (TNF)-α, which further aggravates the prognosis of a SARS-CoV-2 infection (14).

The development and manufacturing of a vaccine against SARS-CoV-2 is an issue of utmost importance, however, it must be taken into consideration that it is going to take

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numerous months to produce a vaccine. Although several companies have announced that a vaccine against COVID-19 will be ready soon, this will be quite difficult to accomplish in reality considering that short- and long-term safety have to be taken into account (15).

Materials and methods

A retrospective observational study on confirmed SARS-CoV-2 patients admitted to 'Sf. Parascheva' Clinical Hospital of Infectious Diseases, Iasi, Romania was conducted between March 4th (the first such admission) and June 30th (the writing of the article). The primary inclusion criteria of the patients in the present study was represented by confirmed SARS-CoV-2 infection tested by RT-PCR assay which had as associated diagnosis type 1 or 2 DM. Patients that did not have a history of DM type 1 or 2 and/or had a negative result with RT-PCR testing were excluded from the present study.

The following data were collected: Demographic data, medical history, clinical and paraclinical data, blood tests, administered treatment and outcome. The RT-PCR tests were performed by either a molecular biology hospital laboratory or other accredited laboratories from Iasi county, Romania.

Results

From the beginning of the outbreak, a total of 1,080 patients were admitted to 'Sf. Parascheva' Clinical Hospital of Infectious Diseases of Iași, Romania. Of these patients, 85 (7.87%) were known to be suffering from DM, mostly type 2 (82 cases, 96.46%). Diabetic patients between 51-70 years old were the most affected by the SARS-CoV-2 infection, the mean age being 62 (Fig. 1), and they presented in fairly equal proportions gender wise (42 were men, 49,41%).

Other associated pathologies were cardiovascular (hypertension, heart failure, and atrial fibrillation), neurological (stroke, epilepsy), neoplastic, renal (kidney failure with or without chronic dialysis) (Fig. 2).

From the total of 1,080 patients admitted, 78 cases involving patients with associated underlying diseases, intensive care unit (ICU) therapy was required. Of these cases, 17 patients had DM as one of the underlying diseases. The majority of these patients (64 cases), presented with oxygen desaturation (Sp02 <89%), were dyspneic and polypneic, or they became hemodynamically unstable with their arterial pressure level dropping below 85/50 mmHg. Fifty-nine patients ultimately required orotracheal intubation and mechanical ventilation due to multiple complications including aspiration bronchopneumonia, sepsis, and multiple organ dysfunction syndrome (MODS).

In addition, in all cases, chest CTs revealed lesions specific for SARS-CoV-2 infection, described either as ground-glass opacities or 'crazy paving' area patterns, linear densities or consolidations.

The treatment was administered according to the international and national guidelines available at the time and included hydroxychloroquine (HCQ)/lopinavir + ritonavir/enoxaparin sodium/tocilizumab/antibiotherapy. Each patient received individualized treatment based on the clinical and paraclinical data, as well as taking into consideration medical interactions. During hospitalization, the management of associated cardiovascular, neurologic, neoplastic and renal comorbidities was ensured, alongside antibiotic treatment to address other types of infectious diseases whenever present, including urinary tract infections, sepsis, cellulitis, and *Clostridium difficile* infection. In addition, psychological therapy was performed upon request (16,17).

Regarding the paraclinical data of patients with DM, glycemic levels over 200 mg/dl were observed in all the cases at the admittance and a median glycated hemoglobin level of 7.2% was calculated.

We took into consideration two groups of patients admitted to the ICU, group A, patients without DM (61 patients) and group B, patients with DM (17 patients). The fatality rate among the patients in group B was considerably higher (88,23%, 15 patients) than the rate of mortality among group B (59.01%, 36 patients) (Fig. 3).

Regarding the glycemic levels of the patients with DM admitted to the ICU correlated with the level of C reactive protein (CRP), it was observed that CRP values >70 mg/l were encountered in the patients that deceased. Patients admitted to the ICU with a CRP <70 mg/l (patient 16 and 17) survived and were later transferred to the clinic (Fig. 4).

Discussion

The latest studies in scientific literature have been revealing a noteworthy association between increased mortality and morbidity in patients with SARS-CoV-2 and advanced age, severe obesity (BMI ≥40 kg/m^2), hypertension and DM as underlying diseases (8,10,14,18,19). In the general population, the prevalence of DM is 8.5% (20) and among the admitted patients considered for the present study it was 7.87%. In addition, the literature states that, elder patients are more affected by DM and often by other comorbidities, especially after the age of 60 (21-23), a fact that can also be sustained by the present study in which >50% of the patients (56.47%) were >60 years old. If we take into consideration that hypertension as well as cardiovascular disease are prevalent in DM patients, it is unclear whether DM independently contributes to this increased risk. However, diabetes has already been frequently reported to be associated with poor prognosis in other respiratory viral infections, mainly seasonal influenza, pandemic influenza A H1N1, SARS, and MERS (24,25).

In March 2020, an Italian health institute reported 2,003 patients that succumbed from SARS-CoV-2 infection (26). Their median age was 80.5, which was considerably higher than the median age 67.84 of the patients included in the present study. In addition, the same study stated that the prevalence of diabetes was 35.5% and that 70% of the total number of patients were men (26), while in our study gender differences were negligible (49.41% patients were men). Furthermore, in the largest case series reported by the Chinese Center for Disease Control and Prevention, performed on 72,314 cases of COVID-19, the patients with DM had a higher mortality (7.3% in DM vs. 2.3% overall) (9).

Moutschen *et al* (27) and Knapp *et al* (28) acknowledge that poorly controlled diabetes inhibits lymphocyte proliferation, and also modifies the functions of neutrophils and

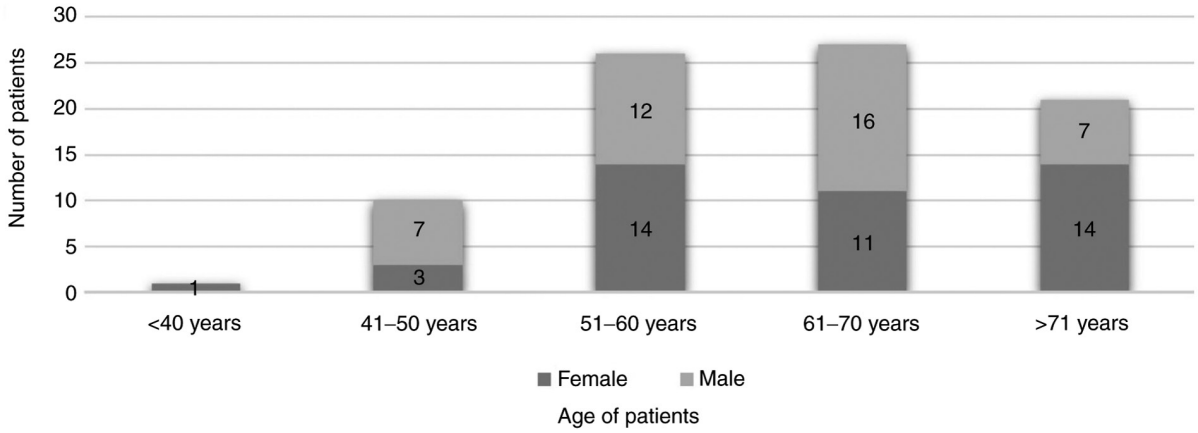

Figure 1. SARS-CoV-2 patient distribution by age and sex.

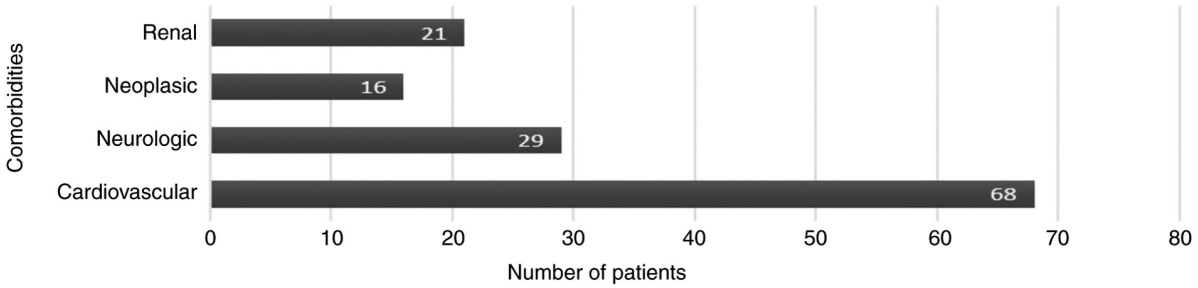

Figure 2. Other associated pathologies in SARS-CoV-2 DM patients. DM diabetes mellitus.

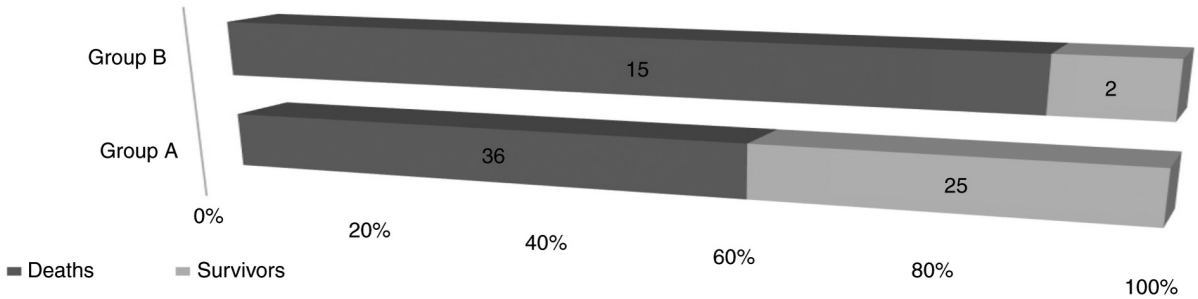

Figure 3. Distribution of the number of deaths and survivors with DM and without DM in SARS-CoV-2 patients admitted to the ICU. Group A, patients without DM; Group B, patients with DM. ICU, intensive care unit; DM diabetes mellitus.

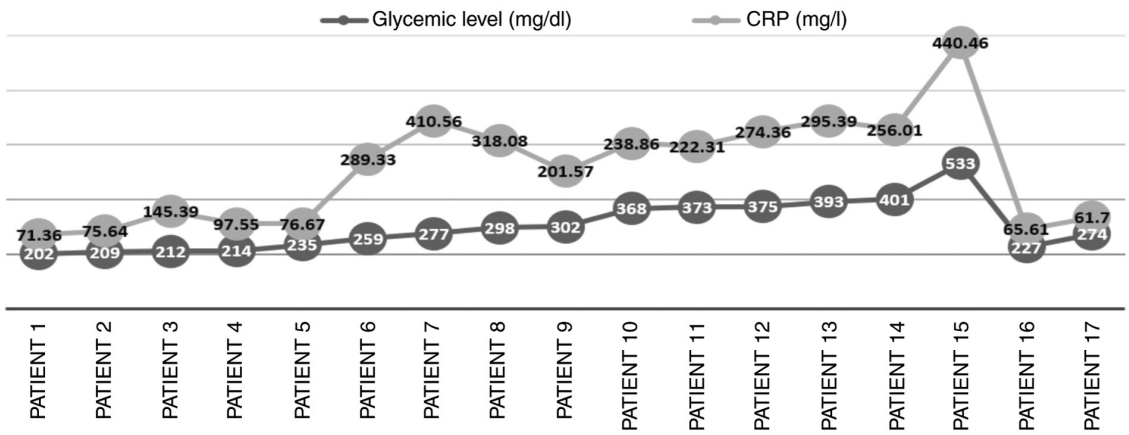

Figure 4. Association between the glycemic level and CRP in SARS-CoV-2 patients with DM admitted to the ICU. C reactive protein; DM diabetes mellitus; ICU, intensive care unit.

monocytes/macrophages. Studies (29,30) performed *in vitro* demonstrated that pulmonary epithelial cells respond to high glucose levels by significantly facilitating the replication of influenza virus. This indicates that hyperglycemia may contribute to increased viral replication *in vivo* (31), which can also apply to the case of the SARS-CoV-2 virus.

Furthermore, endothelial dysfunction and increased platelet aggregation have been associated with type 2 DM and insulin resistance. These are flaws which support the development of a hypercoagulable pro-thrombotic state (32). Last but not least, patients with diabetes have also been revealed to have diminished forced vital capacity (FVC) and forced expiratory volume in one second (FEV1), which is associated with increased plasma glucose levels (33). This may explain the increased number of patients that required ICU therapy (42.35%) and also the increased fatality rate of the patients with underlying DM.

Multiple studies (7,34-36) have determined the serum concentration of CRP in patients with COVID-19 and the results revealed that increased levels of CRP were observed in up to 86% of severe COVID-19 patients. CRP was found at increased levels in the severe group at the initial stage than those in the mild group (35) and also Luo *et al* observed in their study that patients who succumbed to COVID-19 had approximately 10-fold higher levels of CRP than the recovered patients (37). In the present study, the patients admitted to the ICU that succumbed had an increase of CRP value between 14-88-fold (71.36-440.46 mg/l).

In conclusion, uncontrolled DM appears to be a significant predictor of mortality, not only because of how it modifies physiological mechanisms but also by how it predisposes the patient to multiple complications. However, even in the presence of advanced age and DM, 82.35% from the total number of the patients included in the study were cured. Careful assessment of the numerous components that contribute to poor prognosis of the patients with diabetes infected with SARS-CoV-2 virus may represent the best way to overcome the current situation.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary files.

Authors' contributions

CM and GAL designed the study. DN and AV contributed to data extraction and quality assessment. CM, DN and GAL were responsible for the analysis and discussion of the data. CM and GAL drafted the manuscript. AV and DN critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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