Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Cardiac injury prediction and lymphocyte immunity and inflammation analysis in hospitalized patients with coronavirus disease 2019 (COVID-19)☆

Wenqian Zhou a, Ling Song a, Xiang Wang a, Zheng Xu a, Shudong Wang a, Jiqun Wang a, He Xu b, Yang Zheng a,⁎, Yushi Wang a,⁎

a The Center of Cardiovascular Diseases, the First Hospital of Jilin University, Changchun 130021, China
b Department of Respiratory Medicine, the First Hospital of Jilin University—the Eastern Division, Changchun 130031, China

A R T I C L E   I N F O

Article history:
Received 19 April 2020
Received in revised form 11 October 2020
Accepted 15 October 2020
Available online 22 October 2020

Keywords:
Coronavirus disease 2019
Cardiac injury
Lymphocyte immunity
Inflammation

A B S T R A C T

Background: Coronavirus disease 2019 (COVID-19) is an ongoing global pandemic. The ability to predict cardiac injury and analyze lymphocyte immunity and inflammation of cardiac damage in patients with COVID-19 is limited. We aimed to determine the risk factors and predictive markers of cardiac injury in these patients.

Methods: Data from 124 consecutive hospitalized patients with confirmed COVID-19 were collected. We compared the proportion of cardiovascular disease history in moderate, severe, and critical cases. We obtained high-sensitivity cardiac troponin I (hs-cTn I) results from 68 patients. Patients were divided into two groups based on positive hs-cTn I result: those with cardiac injury (n = 19) and those without cardiac injury (n = 49).

Results: Compared with the group with moderate disease, hypertension, coronary heart disease, and smoking were more common in severe and critical cases. Diabetes mellitus was most common in the critical group. Age older than 65 years, presence of chronic kidney disease, and lower blood lymphocyte percentage were independent risk factors of cardiac injury. The total T- and B-lymphocyte counts and CD4+ and CD8+ T-cell counts were significantly lower in those with cardiac injury. A minimal lymphocyte percentage < 7.8% may predict cardiac injury. The interleukin (IL) 6 level in plasma was elevated in the group with cardiac injury.

Conclusions: The lymphocyte percentage in blood may become a predictive marker of cardiac injury in COVID-19 patients. The total T and B cells and CD4+ and CD8+ T-cell counts decreased and the IL-6 level increased in COVID-19 patients with cardiac injury.

© 2020 Published by Elsevier B.V.

1. Introduction

Coronavirus disease 2019 (COVID-19) is a worldwide pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and many patients have died across the globe. The outbreak was declared a Public Health Emergency of International Concern on January 30, 2020, by the World Health Organization (WHO). Although most patients with COVID-19 have respiratory symptoms, reports have suggested that coronavirus can also cause acute cardiac injury [1–3]. The demand for greater understanding of the clinical characteristics of cardiovascular injury in COVID-19 and its associated risk factors and mechanisms is increasing. The aim of this study was to compare the minimal levels of lymphocyte percentage during the disease to determine whether these values could predict cardiac injury.

2. Methods

We retrospectively collected data from 124 hospitalized patients with COVID-19 at Tongji Hospital of Tongji Medical College Hua Zhong University of Science & Technology—Zhongfa Division, China, from January 28, 2020 to March 28, 2020, including medical history, clinical manifestation, laboratory findings, complications, and outcomes data. All the patients in this study had confirmed diagnoses of COVID-19 according to the 7th edition guideline [4] issued by the National Health Commission of China. Patients who were suspected cases were excluded. Of the COVID-19 patients included, 68 had high-sensitivity cardiac troponin I (hs-cTn I) test results. We divided the patients into two groups based whether the hs-cTn I level was above 99th percentile upper limit of the normal reference (14 pg/mL). Moreover, 23 of the
68 cases had lymphocyte immunity analysis results. The severity types of COVID-2019 including mild, moderate, severe, and critical cases were defined according to the 7th edition guideline issued by the National Health Commission of China [4]. We did not include mild cases in our study because patients with mild disease were not admitted to hospital.

2.1. Data collection

We collected baseline characteristics (age and sex), chronic disease history, and clinical data (laboratory findings, complications, intensive care unit–associated treatment, and outcomes). Patients were divided into two groups based on the results of hs-cTn I.

2.2. Approval

This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Ethics Committee of the First Hospital of Jilin University (2020—320). Informed consent was not required because of the retrospective design of the study.

2.3. Statistical analysis

Continuous variables were presented as mean (standard deviation) or median (interquartile range [IQR]) according to normal distribution. Categorical variables were expressed as proportions (%). The continuous variables of two groups were compared using t-test or Mann–Whitney U test according to the data. We used the Kruskal–Wallis test to compare the continuous variables of multiple groups. Categorical variables were compared using the chi-squared or Fisher’s exact test. Logistic regression models were used to define the independent risk factors for cardiac injury of COVID-19 patients. The receiver operating characteristic curve was used to determine the sensitivity and specificity of lymphocyte percentage for estimating cardiac injury.

Statistical analyses were performed using SPSS version 24.0 (IBM, Armonk, NY, USA). Statistical charts were generated using GraphPad Prism 8.0 (GraphPad, San Diego, CA, USA). For all data, p<0.05 was considered statistically significant.

3. Results

Of the 124 patients, 64 (52%) were men and 60 (48%) were women. The median age was 63 years (range, 30–86 years). Forty-four (35%), 62 (50%), and 18 (15%) patients were diagnosed as moderate, severe, and critical cases, respectively. Of the 68 confirmed COVID-19 patients with hs-cTn I results, 19 (28%) had cardiac injury and 49 (72%) did not have cardiac injury. There were 23 patients with peripheral blood immunological tests.

3.1. Cardiovascular disease–associated risk factors (hypertension, diabetes mellitus, coronary heart diseases, smoking) in 124 patients with COVID-19

The proportions of moderate, severe, and critical cases with hypertension were 13.6%, 43.5%, and 50%, respectively (p<0.05). The proportions of patients with diabetes were 13.6%, 22.6%, and 50%, respectively (p<0.05). The proportion of patients with coronary heart disease were 2.3%, 11.3%, and 11.1%, respectively (p<0.05), and the proportion of those who smoked in each group were 2.3%, 19.4%, and 16.7%, respectively (p<0.05). Thus, hypertension, coronary heart disease, and smoking were more common in severe and critical cases. Diabetes was more common in critical cases than in the other two groups (p<0.05) (Supplementary Fig. 1).

3.2. Hs-cTn I results in the moderate, severe, and critical groups

We collected the hs-cTn I results of 68 patients, including 16 (24%) moderate cases, 36 (56%) severe cases, and 16 (24%) critical cases. The median peak levels of hs-cTn I of the three groups were 2.35 [IQR, 1.9–7.4], 4.45 [IQR, 1.9–9.9], and 56.6 [IQR, 24.1–362.9] pg/mL, respectively (p<0.05). The peak hs-cTn I level was significantly higher in the critical group than that in the other two groups (Supplementary Fig. 2).

3.3. Baseline clinical characteristics and laboratory findings of 68 COVID-19 patients

The study included 68 hospitalized confirmed COVID-19 cases with hs-cTn I results. The hs-cTn I level higher than 14 pg/mL was considered positive. Patients were divided into two groups according to the hs-cTn I results: with cardiac injury (n = 19, 28%) and without cardiac injury (n = 49, 72%).

The proportion of patients older than 65 years was significantly higher in those with cardiac injury than in those without cardiac injury. Moreover, patients with cardiac injury were more likely to have diabetes and chronic kidney disease (CKD), but not other comorbidities, including smoking, hypertension, coronary heart disease, chronic liver disease, chronic respiratory disease, thyroid disease, cancer, and influenza. Regarding laboratory findings, lymphocyte percentage and minimal lymphocyte percentage were much lower in patients with cardiac injury than in those without cardiac injury. Elevated interleukin (IL) 6 and creatinine were higher in those with cardiac injury than in those without cardiac injury. In addition, the N-terminal pro-B-type natriuretic peptide level was much higher in those with cardiac injury than in those without cardiac injury (Table 1).

Patients with cardiac injury were more common in the critical group. Moreover, patients with cardiac injury required more non-invasive and invasive mechanical ventilations. More patients had multiple-organ dysfunction syndrome and died in the group with cardiac injury than in the group without cardiac injury (Table 1).

3.4. Multivariable logistic regression analysis of risk factors in cardiac injury patients

Risk factors that were significantly different in the two groups were analyzed by multivariable logistic regression, including age, diabetes, chronic kidney disease, lymphocyte percentage, minimal lymphocyte percentage, creatinine, and IL-6. Age ≥ 65 years, CKD, and minimal lymphocyte percentage were independent risk factors for cardiac injury (Supplementary Table 1).

3.5. Blood lymphocyte percentage in patients with cardiac injury

The blood lymphocyte percentages (%) were compared at four main time points (days 1, 8, 18, and 23, ±2 days) after admission (Fig. 1A). The lymphocyte percentage in the group with cardiac injury was significantly lower than that in the group without cardiac injury at four time points (median [IQR]: 11.2% [8.2–16.2] vs. 23.3% [14.7–29.9], p = 0.002; 9.0% [5.4–23.9] vs. 22.6% [16.5–33.1], p = 0.002; 11.8% [3.57–20.7] vs. 24.4% [18.2–27.8], p = 0.004; 12.2% [2.8–25.4] vs. 26.1% [23.3–30.3], p = 0.009, respectively). The minimal lymphocyte percentages during the disease were compared to predict cardiac injury. These values could predict cardiac injury with relative accuracy (p = 0.000, area under the curve = 0.803; Fig. 1B). The optimal cutoff for minimal lymphocyte percentage was 7.8%.

3.6. Lymphocyte immunological features of COVID-19 patients with and without cardiac injury

The lymphocyte immunological features in the peripheral blood of 23 patients with COVID-19 were analyzed, including 8 patients with...
Table 1: Baseline Clinical Characteristics and Laboratory Findings of 68 COVID-19 Patients.

| Characteristics               | All patients (n = 68) | With cardiac injury (n = 19) | Without cardiac injury (n = 49) | p Value |
|-------------------------------|-----------------------|-----------------------------|--------------------------------|---------|
| Age, years, median (range)    | 67 (30–86)            | 73 (57–86)                  | 64 (30–79)                     |         |
| Age group, n (%)              | 20–49 years 10 (15%)  | 0 (0%)                      | 10 (20%)                       | 0.001   |
|                               | 50–65 years 19 (28%)  | 2 (11%)                     | 17 (35%)                       |         |
|                               | ≥65 years 39 (57%)    | 17 (89%)                    | 22 (45%)                       |         |
| Sex                           | Male, n (%) 34 (50%)  | 6 (32%)                     | 28 (57%)                       | 0.052   |
|                               | Female, n (%) 34 (50%)| 13 (68%)                    | 21 (43%)                       |         |
| Smokers, n (%)                | 13 (19%)              | 2 (11%)                     | 11 (22%)                       | 0.223   |
| Chronic disease, n (%)        | Hypertension 29 (43%) | 11 (58%)                    | 18 (37%)                       | 0.095   |
|                               | Diabetes 16 (24%)     | 8 (42%)                     | 8 (16%)                        | 0.03    |
|                               | Coronary heart disease| 8 (18%)                     | 3 (16%)                        | 0.395   |
|                               | Chronic kidney disease| 7 (10%)                    | 6 (32%)                        | 0.001   |
|                               | Chronic liver disease | 4 (6%)                      | 2 (11%)                        | 0.317   |
|                               | Chronic respiratory disease| 6 (8%)                | 2 (11%)                        | 0.541   |
|                               | Thyroid disease 5 (7%)| 2 (11%)                     | 3 (6%)                         | 0.431   |
|                               | Cancer 4 (6%)          | 1 (5%)                      | 3 (6%)                         | 0.69    |
|                               | Flu accompanied, n (%)| 24 (35%)                    | 7 (37%)                        | >0.05   |
| Heart rate, bpm, mean ± SD    | 89 ± 16               | 91 ± 15                     | 88 ± 16                        | 0.357   |
| Laboratory findings, median (IQR) | Leukocytes, 10^9/L | 6.45 (5.22–7.96) | 6.48 (5.24–8.95) | 6.41 (5.24–7.70) | 0.217 |
|                               | Lymphocyte percentage | 20.4 (11.1–27.4) | 11.2 (8.2–16.2) | 23.3 (14.7–29.9) | 0.004 |
|                               | Minimal lymphocyte percentage | 16.2 (10.15–26.65) | 6.7 (3.2–16.2) | 20.3 (12.3–29.0) | 0.000 |
|                               | Albumin, g/L 36.6 (32.8–19.7) | 33.8 (32.1–37.7) | 37.9 (33.8–40.3) | 0.05   |
|                               | Alanine aminotransferase, U/L | 29 (22–37.5) | 35 (28–57) | 25.5 (19–34) | <0.05 |
|                               | Aspartate aminotransferase, U/L | 31 (20–49) | 30 (19–49) | 31 (19–49) | >0.05 |
|                               | Creatinine, μmol/L | 73 (62–88)                  | 91 (66–108)                    | 69 (62–79) | 0.043 |
|                               | C-reactive protein, mg/L| 7.5 (1.9–27.6) | 24.4 (2.5–100.2) | 6.5 (1.9–19.1) | 0.319 |
|                               | Erythrocyte sedimentation rate, mm/H | 35 (17–68) | 38 (30–73) | 26 (14–62) | 0.102 |
|                               | IL-6, pg/mL | 4.0 (2.7–3.5) (n = 47) | 8.2 (4.4–30.2) (n = 12) | 3.5 (2.7–6.5) (n = 35) | 0.048 |
|                               | TNF-α, pg/mL | 7.5 (6.0–10.8) (n = 47) | 10.2 (6.2–12.2) (n = 12) | 7.3 (6.0–8.4) (n = 35) | 0.104 |
|                               | D-dimer increased-No. % | 44 (65%) | 15 (79%) | 29 (59%) | 0.163 |
|                               | NT-proBNP, pg/mL | 127 (53–472) | 614 (295–1833) | 65 (36–195) | 0.000 |
| Severity type, n (%)          | Moderate 16 (24%)     | 1 (5%)                      | 15 (31%)                       | 0.000   |
|                               | Severe 36 (53%)       | 4 (21%)                     | 32 (65%)                       |         |
|                               | Critical 16 (23%)     | 14 (74%)                    | 2 (4%)                         |         |
| ICU associated treatment, n (%)| Noninvasive ventilation 7 (10%) | 6 (32%) | 1 (2%) | 0.001 |
|                               | Invasive ventilation | 6 (9%)                      | 6 (32%)                        | 0 (0%)  | 0.000 |
|                               | Continuous renal replacement therapy 2 (3%) | 2 (11%) | 0 (0%) | 0.075 |
| Complications, n (%)          | SIRS 2 (3%)           | 1 (5%)                      | 1 (2%)                         | 0.484   |
|                               | MODS 7 (10%)          | 6 (32%)                     | 1 (2%)                         | 0.001   |
| Outcome, n (%)                | Discharged 61 (90%)   | 13 (68%)                    | 48 (98%)                       | 0.001   |
|                               | Died 7 (10%)          | 6 (32%)                     | 1 (2%)                         |         |

Values are presented as median (interquartile range), mean ± standard deviation, or number (%).

IL-6, interleukin 6; TNF-α, tumor necrosis factor α; NT-proBNP, N-terminal pro-B-type natriuretic peptide; ICU, intensive care unit; SIRS, systemic inflammatory response syndrome; MODS, multiple-organ dysfunction syndrome.

![Fig. 1. (A) Lymphocyte percentage with or without cardiac injury. (B) Receiver operating characteristic (ROC) curve of minimal lymphocyte percentage.](image-url)
cardiac injury and 15 patients without (Table 2). Compared with cases without cardiac injury, the absolute numbers of total T lymphocytes, total B lymphocytes, CD4+ T cells, and CD8+ T cells were significantly decreased in the group with cardiac injury. The percentages of cases with decreased total T lymphocytes, CD4+ T cells, and CD8+ T cells were higher in the group with cardiac injury than in the group without cardiac injury. The absolute numbers of natural killer (NK) cells showed no significant difference between the two groups.

3.7. Inflammatory biomarkers in plasma of patients with and without cardiac injury

We collected plasma from 47 patients with COVID-19. The plasma levels of the inflammatory biomarker IL-6 was significantly elevated in the group with cardiac injury compared with the group without cardiac injury (median [IQR]: 8.2 [4.4–30.2] vs. 3.5 [2.7–6.5] pg/mL, p = 0.048). There was an up-trend of levels of tumor necrosis factor (TNF) α, IL-2, and IL-8 in the group with cardiac injury. However, the plasma levels of TNF-α, IL-2, and IL-8 did not differ between the two groups (Fig. 2).

3.8. Duration of infection and symptoms with or without cardiac injury as well as severity

The durations of viral shedding and symptoms did not statistically differ between the group with cardiac injury and the group without cardiac injury. In addition, the durations of viral shedding and symptoms were longer in the critical group than in the severe and moderate groups. The mean duration of viral shedding in the critical, severe, and moderate groups were 35 [IQR, 29–39], 25 [IQR, 19–31], and 20 [IQR, 16–24] days, respectively (p < 0.005), and the mean duration of symptoms were 35 [IQR, 25–46], 21 [IQR, 16–27], and 22 [IQR, 16–30] days, respectively (p = 0.05) (Supplementary Fig. 3).

Table 2

| Immunological Features of COVID-19 Patients | All patients (n = 23) | With cardiac injury (n = 8) | Without cardiac injury (n = 15) | p Value |
|-------------------------------------------|----------------------|-----------------------------|-------------------------------|--------|
| Total T lymphocytes (%)                   | 73.23 (65.88–75.94)  | 73.10 (63.21–74.04)         | 73.23 (65.88–76.48)           | 0.506  |
| Total T lymphocytes count/μL             | 1022 (911–1298)      | 598 (492–943)               | 1233 (923–1406)              | 0.003  |
| Decreased, n (%)                         | 11 (48%)             | 7 (88%)                     | 4 (27%)                      | 0.009  |
| Total B lymphocytes (%)                  | 12.20 (9.14–17.73)   | 12.42 (9.48–16.18)          | 12.20 (9.35–17.36)           | 0.825  |
| Increased, n (%)                         | 4 (17%)              | 2 (25%)                     | 2 (13%)                      | 0.589  |
| Total B lymphocytes count/μL            | 151 (112–216)        | 112 (67–162)                | 170 (132–283)                | 0.003  |
| Decreased, n (%)                        | 4 (17%)              | 3 (37.5%)                   | 1 (6.7%)                     | 0.103  |
| CD4+ cells count/μL                     | 43.20 (37.22–48.08)  | 41.46 (35.77–48.70)         | 43.2 (37.64–46.31)           | 0.776  |
| Decreased, n (%)                        | 10 (43%)             | 6 (75%)                     | 4 (27%)                      | 0.039  |
| CD8+ cells (%)                          | 24.54 (21.19–27.93)  | 22.40 (13.61–27.77)         | 24.86 (22.66–27.93)          | 0.294  |
| Decreased, n (%)                        | 10 (43%)             | 6 (75%)                     | 4 (27%)                      | 0.039  |
| NK cells (%)                            | 14.17 (10.78–23.28)  | 16.48 (12.62–26.14)         | 13.51 (9.91–20.49)           | 0.357  |
| Decreased, n (%)                        | 9 (39%)              | 5 (63%)                     | 4 (27%)                      | 0.179  |
| Th/Ts                                    | 1.80 (1.40–2.34)     | 1.98 (1.80–2.50)            | 1.66 (1.31–2.02)             | 0.357  |

Values are presented as median [interquartile range] or n (%). COVID-19, coronavirus disease 2019; NK, natural killer cells; Th/Ts, helper T cells/suppressor T cells.
COVID-19 patients, including the heart [11]. However, after infection, SARS-CoV-2 reduces ACE2 activity and consumes the receptors [14]; hence, the ACE2/AngII balance is disturbed and the heart may not be protected anymore, resulting in cardiac injury. This might be the reason why patients with underlying cardiovascular disease were more prone to infection and exhibited severe and critical disease, especially cardiac injury due to ACE2.

Lymphocytes play an important role in immune homeostasis and inflammatory response. Our results showed that the lymphocyte percentage decreased significantly with cardiac injury. A minimal lymphocyte percentage in peripheral blood <7.8% could predict a high risk of cardiac injury in patients with COVID-19. This will be helpful for physicians to judge the heart condition of patients. The probable mechanism of lymphopenia is the presence of ACE2 receptors in lymphocytes, which can be a target for SARS-CoV-2. The virus may also destroy immune organs. An inflammatory response leads to the release of pro-inflammatory cytokines, which in turn reduces the lymphocyte count. Furthermore, patients with cardiac injury were mostly severe and critical cases, with accompanying hyperlactic acidemia, which could inhibit the proliferation of lymphocytes [15].

Data from other reports have suggested that older adults were more susceptible to COVID-19, and aging is strongly associated with infection fatality in COVID-19 [16]. Our results showed that age ≥65 years was a risk factor for cardiac injury. A possible mechanism of cardiac injury is through immune function disruption. The immune system of older patients undergoes many age-related changes, known as immune senescence [17]. Lymph nodes, which produce naive T and B cells, become less able to maintain naive T cells and differentiation in the final third of life. B cells also undergo a similar reduction but much more slowly than T cells [18]. This is consistent with the immunological analysis results in this study, which suggested that the numbers of T and B lymphocytes were significantly decreased in the group with cardiac injury, but the decreased proportion of B lymphocytes did not differ. Another problem in the immune system is that T cells cannot move quickly to “fight” due to dysregulation of chemokines, which guide T-cell migration. Therefore, aging is associated with cardiac injury, probably due to immune senescence.

SARS-CoV-2 infection can cause inflammatory cytokine storms in the immune system. In this study, we compared several inflammatory biomarkers between the groups with and without cardiac injury. The IL-6 level was elevated in the group with cardiac injury, but this was not the case with other biomarkers. The reason might be because cardiac damage was related to aging and immune dysregulation. Thus, the inflammatory response was not as strong in older people as it was in younger people. However, the inflammatory response was still excessive and active at an early stage. Our results showed that more patients had CKD and elevated levels of creatinine in the blood in the group with cardiac injury than in the group without cardiac injury. Therefore, we considered that cytokine overproduction was involved in kidney–heart bidirectional damage in COVID-19 patients. Previous reports suggested that COVID-19 patients with diabetes are affected by a low-grade inflammation that facilitates the cytokine storm, and IL-6 was more elevated in COVID-19 patients with diabetes than in those without diabetes [19]. Therefore, we thought that diabetes resulted in metabolic inflammation and cytokine storms that damaged the heart further. In addition, the imbalance and loss of ACE2 might aggravate the inflammatory cytokine storm [20].

There are some limitations to our study. First, it was a single-center study and the number of patients was not very large. Second, we lacked some echocardiographic information and so did not include echocardiography results. Third, the prognosis in hospital is limited, and we did not follow-up.

In conclusion, the risk factors for cardiac injury in COVID-19 patients include not only aging but also chronic diseases such as diabetes and CKD. These factors affect the immune system and cause an inflammatory response, which damages the heart further. Lymphopenia is an effective marker that might be able to predict cardiac injury in COVID-19 patients and help physicians estimate disease conditions.
Funding
None.

Declaration of Competing Interest
None.

Acknowledgments
We would like to thank Editage (www.editage.cn) for English language editing.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2020.10.049.

References
[1] F. Zhou, T. Yu, R. Du, G. Fan, Y. Liu, Z. Ji, X. Wang, Y. Liang, Y. Wu, Y. Jiang, Z. Chen, X. Zhang, Y. Wang, X. Xu, J. Ma, Y. Wang, Y. Xiong, J. Liu, S. Song, S. Li, J. Xiao, S. Ji, L. Guo, Q. Gao, Q. Guan, G. Wu, D. Xie, J. Shen, Hypersensitivity pneumonitis predicts disease severity of COVID-19: a descriptive and predictive study, Signal Transduct Target Ther. 5 (2020) 33.
[2] Y. Bai, X. Zhang, J. Song, T. Chen, M. Han, S. Li, X. Luo, J. Zhao, Q. Ning, Clinical and immunologic features in severe and moderate coronavirus disease 2019 in China, J. Clin. Investig. https://doi.org/10.1172/JCI113724.
[3] A. Akhmerov, E. Marban, COVID-19 and the heart, Circ. Res. https://doi.org/10.1161/CIRCRESAHA.120.317055.
[4] S.R. Bornstein, R. Dalan, D. Hopkins, G. Mingrone, B.O. Boehn, Endocrine and metabolic link to coronavirus infection, Nat. Rev. Endocrinol. https://doi.org/10.1038/s41574-020-0353-9.
[5] M. Bhatia, A. Boonyasiri, A. Cori, Z. Cucunuba, R. FitzJohn, K. Gaythorpe, W. Green, S. Bhatia, A. Dighe, J.T. Grif, M. Baguelin, M. Derogue, J. Nikolich-Zugich, The twilight of immunity: emerging concepts in aging of the immune system, Nat. Immunol. 19 (2018) 10–19.
[6] J. Nikolich-Zugich, K.S. Knox, C.T. Rios, B. Natt, D. Bhattacharya, M.J. Fain, SARS-CoV-2 and COVID-19 in older adults: what we may expect regarding pathogenesis, immune responses, and outcomes, GeroScience (2020) https://doi.org/10.1007/s41357-020-00186-0.
[7] E. Maddaloni, R. Buzzetti, Covid-19 and diabetes mellitus: unveiling the interaction of two pandemics, Diabetes Metab. Res. Rev. https://doi.org/10.1002/dmrr.3321 e33213321.
[8] M. Gheblawi, K. Wang, A. Viveiros, Q. Nguyen, J.C. Zhong, A.J. Turner, M.K. Raizada, M.B. Grant, G.Y. Oudit, Angiotensin converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system, Circ. Res. https://doi.org/10.1161/CIRCRESAHA.120.317015.