ORIGINAL ARTICLE

New Insights on the Mechanisms of Myocardial Injury in Hypertensive Patients With COVID-19

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Abstract

Purpose Myocardial injury is common in hypertensive patients with 2019 coronavirus disease (COVID-19). Immune dysregulation could be associated to cardiac injury in these patients, but the underlying mechanism has not been fully elucidated.

Methods All patients were selected prospectively from a multicenter registry of adults hospitalized with confirmed COVID-19. Cases had hypertension and myocardial injury, defined by troponin levels above the 99th percentile upper reference limit, and controls were hypertensive patients with no myocardial injury. Biomarkers and immune cell subsets were quantified and compared between the two groups. A multiple logistic regression model was used to analyze the associations of clinical and immune variables with myocardial injury.

Results The sample comprised 193 patients divided into two groups: 47 cases and 146 controls. Relative to controls, cases had lower total lymphocyte count, percentage of T lymphocytes, $CD8^+CD38^+$ mean fluorescence intensity (MFI), and percentage of $CD8^+$ human leukocyte antigen DR isotope $(HLA-DR)^+ CD38^-$ cells and higher percentage of natural killer lymphocytes, natural killer group 2A $(NKG2A)^+$ MFI, percentage of $CD8^+CD38^+$ cells, $CD8^+HLA-DR^+MFI$, $CD8^+NKG2A^+MFI$, and percentage of $CD8^+HLA-DR^-CD38^+$ cells. On multivariate regression, the $CD8^+HLA-DR^+MFI$, $CD8^+CD38^+MFI$, and total lymphocyte count were associated significantly with myocardial injury.

Conclusion Our findings suggest that lymphopenia, $CD8^+CD38^+MFI$, and $CD8^+HLA-DR^+MFI$ are immune biomarkers of myocardial injury in hypertensive patients with COVID-19. The immune signature described here may aid in understanding the mechanisms underlying myocardial injury in these patients. The study data might open a new window for improvement in the treatment of hypertensive patients with COVID-19 and myocardial injury.

Introduction

The 2019 coronavirus disease (COVID-19) pandemic has been the deadliest viral outbreak to occur in decades, causing more than 6 million deaths worldwide as of October 2022 [1]. At the beginning of the pandemic, the respiratory tract was identified as the principal target of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), but

it is currently known that other major organs, such as the heart, can be affected [2]. Cardiac comorbidities, particularly hypertension, are highly prevalent in patients hospitalized with COVID-19 and are related directly to the risk of clinical disease progression [3, 4].

Cardiac injury, defined as significant cardiac troponin elevation, is the most frequently reported cardiac abnormality in patients hospitalized with COVID-19, with a prevalence ranging from 7 to 44% [5–7]. Our group and others have identified the troponin level as an important risk predictor

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for these patients, capable of discriminating between those with low and increased mortality rates. Diverse forms and mechanisms of myocardial injury, including acute myocardial ischemia due to plaque rupture, oxygen supply/demand imbalance (types 1 and 2 infarction), non-ischemic injuries such as myocarditis, direct virus-mediated injury, and immune system dysregulation, have been described in patients with COVID-19 [8, 9]. Myocardial injury is more prevalent in older patients and those with less oxygen saturation, diabetes, hypertension, or other cardiovascular comorbidities.

Among the comorbidities associated with COVID-19 and myocardial injury, hypertension is particularly important due to its high prevalence and global burden, but the mechanism of this association and the reasons for clinical progression have not been elucidated clearly [10, 11]. Considering that myocardial injury due to direct SARS-CoV-2 infection is rare and that the immune system is often dysregulated in patients with COVID-19, and cytokine storm and lymphopenia are important immune markers of progression to severe disease [12–14], we investigated the immune profile of hypertensive patients with COVID-19 and myocardial injury aiming to obtain a better understanding of the immune dysregulation and to provide new insights on the mechanism of myocardial injury in hypertensive patients with this disease.

Methods

Patients included in this case-control study were selected prospectively from a multicenter registry of adult patients hospitalized with confirmed COVID-19 diagnoses in 10 tertiary hospitals in Brazil between November 2020 and December 2021. SARS-CoV-2 infection was confirmed by real-time reverse-transcription polymerase chain reaction of nasopharyngeal and/or oropharyngeal swab samples. Cases were hypertensive patients with myocardial injury, defined by troponin levels exceeding the 99th percentile upper reference limit, and controls were hypertensive patients without myocardial injury. Blood samples were collected in the first week of hospitalization. The protocol was approved by the institutional review boards and ethics committees at participating sites (CAAE#34035120.1.0000.5249). All patients provided written informed consent before enrollment.

Trained investigators collected demographic, clinical, and laboratory data using the standardized form from the International Severe Acute Respiratory and Emerging Infection Consortium/World Health Organization Clinical Characterization Protocol [15]. Data were collected from electronic medical records and entered into electronic case-report forms using the Research Electronic Data Capture platform (Vanderbilt University, Nashville, TN, USA). Clinical data included data on comorbidities, complications, and treatment. Laboratory tests were performed throughout hospitalization according to local clinical practice. The patients were followed prospectively until hospital discharge or in-hospital death. They were categorized according to age (< 50, 50–69, and ≥ 70 years), sex, body mass index (BMI), oxygen saturation ($> 93\%$ and $\leq 93\%$), and the presence of diabetes and cardiac and other comorbidities.

Biomarker Quantification

Plasma samples were separated after centrifugation and then frozen and stored at -20 °C until analysis. Circulating levels of cytokines were measured using the MILLIPLEX MAP human cytokine/chemokine magnetic bead panel (#HCYTMAG-60 K-PX29; Merck Millipore, Billerica, MA, USA) according to the manufacturer's instructions. The C-reactive protein level was measured by latex-enhanced immunoturbidimetric assay. Cytokines not detected in $> 50\%$ of the patient samples were excluded from further analyses.

Peripheral Blood Mononuclear Cell Isolation

Blood samples collected into ethylenediaminetetraacetic acid (EDTA) tubes (BD Vacutainer® spray-coated K2EDTA tube; Becton, Dickinson and Company, Franklin Lakes, NJ, USA) were centrifuged at $1500 \times g$ for 15 min at 21 °C. Lymphocytes and monocytes were quantified by photometry using an automized ABX Micros 60 system (Horiba Medical, Montpellier, France). To obtain peripheral blood mononuclear cells (PBMCs), density gradient centrifugation (Ficoll-Paque; GE Healthcare, Piscataway, NJ, USA) was performed, as previously described [14].

Flow Cytometry

To quantify the immune cell populations in the PBMCs, 1×10^6 cells were stained with various combinations of fluorophore-conjugated antibodies, as previously described [14]. The following profiles were quantified: total monocytes, total lymphocytes, B lymphocytes, T lymphocytes, natural killer (NK) cells, CD4+ T cells, CD8+ T cells, CD4/CD8 cell ratio, CD8+ CD38+ T cells [percentage and CD38 mean fluorescence intensity (MFI)], CD8+ human leukocyte antigen DR isotope (HLA-DR)+ T cells (percentage and HLA-DR MFI), CD8+ natural killer group 2A (NKG2A)+ T cells (percentage and NKG2A MFI), CD8+ HLA-DR+ CD38− T cells, CD8+ HLA-DR+ CD38+ T cells, CD8+ HLA-DR− CD38+ T cells, and CD8+ HLA-DR− CD38− T cells. The approximate membrane expression (MFI) of the antigens HLA-DR and CD38, important markers of T-cell

activation, and of NKG2A, an inhibitory T-cell receptor, was evaluated to improve the understanding of lymphocyte properties.

Statistical Analysis

Categorical variables, including continuous clinical variables categorized according to traditional cut-off points (age, oxygen saturation, and BMI), were characterized as proportions. Fisher's exact test was used to compare the frequencies of clinical variables between groups with and without myocardial injury. Continuous variables were described as medians, means, and standard deviations, and compared between cases and controls using the Mann–Whitney test. To assess the magnitude of variable associations, Cohen's effect sizes (d values) were calculated. Pearson correlation (r) was performed to assess correlations among cytokines and immune cell subsets. Immune marker data were log transformed and standardized, and multivariate forward automatic stepwise logistic regression analysis was performed to identify variables associated with myocardial injury. Variables showing significant associations were dichotomized using 90% sensitivity cut-off points, and receiver operating characteristic (ROC) curves were used to assess their value in discriminating between cases and controls. To assess correlations between baseline clinical and selected immune biomarkers according to the presence or absence of myocardial injury, phi (φ) correlation coefficients were calculated. To quantify the associations of the selected clinical and immune variables with myocardial injury, a multiple logistic regression model was used and adjusted, and unadjusted odds ratios and 95% confidence intervals were calculated. All analyses were performed using SPSS software (version 24.0; IBM Corporation, Armonk, NY, USA).

Results

In total, 193 hypertensive patients with COVID-19 were enrolled in this study: 47 cases with myocardial injury and 146 controls without myocardial injury. The median time of the blood collection was 3.0 and 2.0 days after hospitalization for the patients with and without myocardial injury, respectively. The cases were predominantly male, but the sex distribution did not differ significantly between groups. The cases were older than controls, had lower oxygen saturation values, and were more overweight but not obese. In addition, larger proportions of the cases were diabetic; had cardiac comorbidities, including chronic heart disease, heart failure, and coronary and valvular disease; and had other

Table 1 Baseline characteristics of hypertensive patients hospitalized for COVID-19 with and without myocardial injury

Characteristics	Myocardial injury				Fisher's exact test p-value
	No ($n=146$)		Yes ($n=47$)		
	n	(%)	n	(%)	
Sex					
Male	96	(65.8)	35	(74.5)	0.288
Female	50	(34.2)	12	(25.5)	
Age					
< 50 years	56	(38.4)	4	(8.5)	< 0.001
50 to 69.9 years	77	(52.7)	17	(36.2)	
≥ 70 years	13	(8.9)	26	(55.3)	
Oxygen Saturation					
> 93%	123	(84.2)	28	(59.6)	0.001
≤ 93%	23	(15.8)	19	(40.4)	
BMI (kg/m^2)					
< 25	13	(8.9)	9	(19.1)	0.002
25 a 29.9	57	(39.0)	23	(48.9)	
≥ 30.0	76	(52.1)	10	(21.3)	
Diabetes					
No	109	(74.7)	24	(51.1)	0.004
Yes	37	(25.3)	23	(48.9)	
Cardiac comorbidities[a]					
No	136	(93.2)	34	(72.3)	< 0.001
Yes	10	(6.8)	13	(27.7)	
Other comorbidities[b]					
No	142	(97.3)	38	(80.9)	0.001
Yes	4	(2.7)	9	(19.1)	

[a]Chronic heart disease, heart failure, and coronary and valvular disease

[b]Chronic lung disease, asthma, and chronic kidney disease

COVID-19, 2019 coronavirus disease; BMI, body mass index

comorbidities, including asthma, chronic pulmonary disease, and chronic kidney disease (Table 1).

Immune Signatures of Hypertensive Patients With and Without Myocardial Injury

Relative to the controls, the cases had higher IL-ra, IFN-γ, MIP-1α, MIP-1β, IL-17A, IL-12 (p70), TNF-α, and TNF-β levels and lower EGF, eotaxin, MCP-1, and VEGF levels (Fig. 1). A large effect size was observed for EGF ($d=-1.02$; Table S1).

The total lymphocyte count, percentage of T lymphocytes, CD8$^+$ CD38$^+$ MFI, and percentage of CD8$^+$ HLA-DR$^+$ CD38$^-$ cells were lower in patients with than in those without myocardial injury. The percentage of NK lymphocytes,
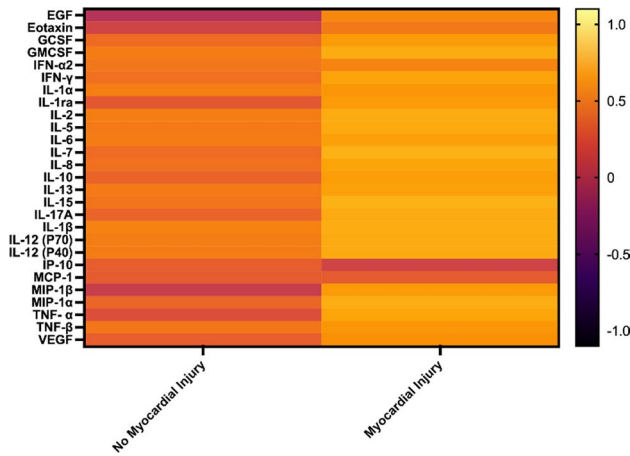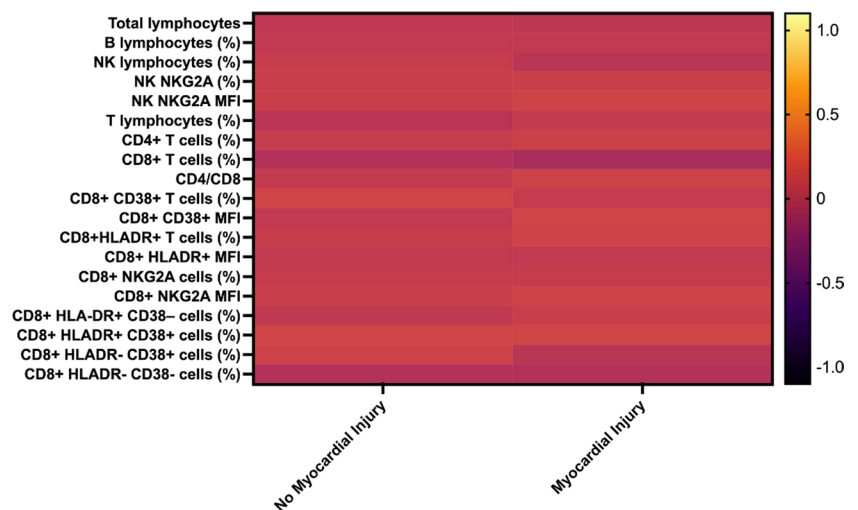
Fig. 1 Log transformed and standardized mean cytokine values in hypertensive patients with Covid-19 with and without myocardial injury. Color scale bar shows a range of log transformed and standardized mean cytokine values. The orange-yellow colors represent higher levels, and dark colors represent lower levels

NK NKG2A MFI, percentage of CD8$^+$ CD38$^+$ cells, CD8$^+$ HLA-DR MFI, CD8$^+$ NKG2A MFI, and percentage of CD8$^+$ HLA-DR$^-$ CD38$^+$ cells were increased in patients with myocardial injury (Fig. 2). Effect sizes were largest for the CD8$^+$ CD38$^+$ MFI ($d = -0.86$), CD8$^+$ NKG2A MFI ($d = 0.96$), and CD8$^+$ HLA-DR MFI ($d = 2.41$; Table S2).

We explored the Pearson correlation between the total cytokines and the different cell subsets in both groups and noticed significant correlations in patients with and without myocardial injury. Although most correlations were weak, significant correlations were more frequent in patients with myocardial injury, and IL-1α was the cytokine that presented the higher number of correlations with the cell subsets studied in this group. In addition, we found moderate correlations between total lymphocyte count with IL-10 and IP-10 in patients with no myocardial injury (-0.512 and -0.408, respectively; Fig. 3).

Best Immune Biomarkers for the Prediction of Myocardial Injury in Hypertensive Patients with COVID-19

Four variables were associated with myocardial injury in the final logistic regression model: the CD8$^+$ HLA-DR MFI ($\beta = 2.62$, $p < 0.001$), EGF concentration ($\beta = -1.15$, $p = 0.014$), CD8$^+$ CD38 MFI ($\beta = -2.18$, $p = 0.002$), and total lymphocyte count ($\beta = -1.39$, $p = 0.004$; Table S3). Areas under ROC curves were 0.940 for CD8$^+$ HLA-DR MFI > 1800, 0.893 for EGF concentration < 196 pg/mL, 0.829 for CD8$^+$ CD38 MFI < 4.700, and 0.752 for total lymphocyte count < 1740 (all $p < 0.001$; Fig. 4). The binary associations of these biomarkers in patients with and without myocardial injury are illustrated in Fig. S1.

Among patients with myocardial injury, significant correlations were detected between age ≥ 70 years and cardiac comorbidities ($\varphi = 0.556$, $p < 0.001$), diabetes and total lymphocyte count < 740 ($\varphi = -0.352$, $p = 0.015$), and CD8$^+$ HLA-DR MFI > 1800 and EGF level < 196 pg/mL ($\varphi = 0.389$, $p = 0.007$). Among patients without myocardial injury, significant correlations were observed between diabetes and oxygen saturation ≤ 93% ($\varphi = 0.180$, $p = 0.029$), diabetes and cardiac comorbidities ($\varphi = 0.216$, $p = 0.009$), and age ≥ 70 years and non-cardiac comorbidities ($\varphi = 0.242$, $p = 0.003$; Table S4).

In a univariate logistic model, myocardial injury was associated significantly with age ≥ 70 years, oxygen saturation ≤ 93%, BMI < 30 kg/m^2, diabetes, cardiac comorbidities, other comorbidities, and the four biomarkers selected by logistic regression. After adjustment, only three biomarkers remained significantly associated with myocardial injury: the CD8$^+$ HLA-DR MFI [adjusted odds ratio (aOR) = 462.78], CD8$^+$ CD38 MFI (aOR = 35.14), and total lymphocytes (aOR = 39.99; Table 2; Fig. 5).

Fig. 2 Log transformed and standardized mean immune cell subsets values in hypertensive patients with Covid-19 with and without myocardial injury. Color scale bar shows a range of log transformed and standardized mean cytokine values. The orange-yellow colors represent higher levels, and dark colors represent lower levels
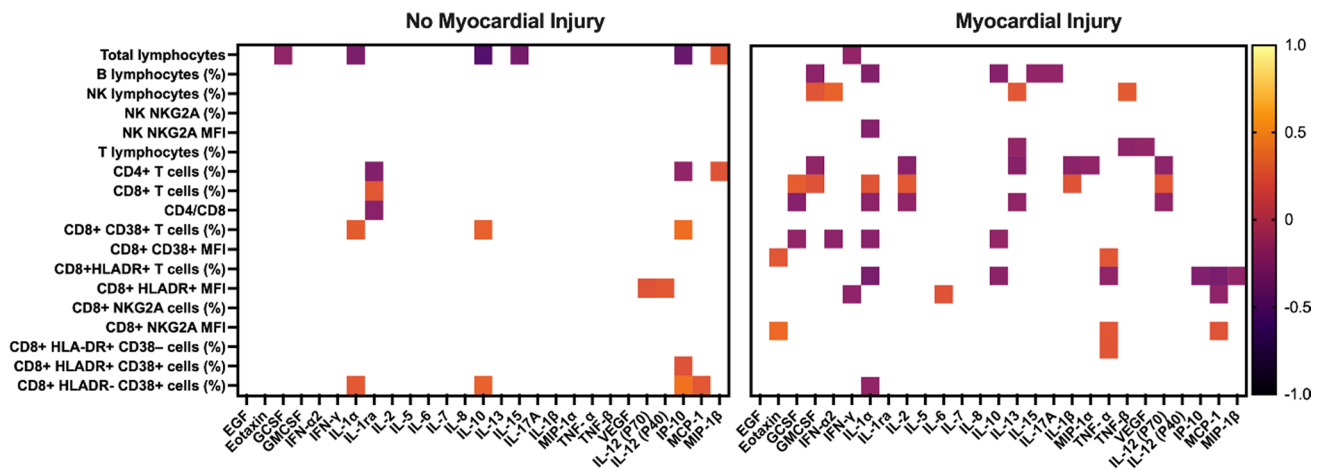
Fig. 3 Heat map of correlations among log transformed and standardized immune cell subsets and cytokines in hypertensive patients with Covid-19 with and without myocardial injury. Color scale bar shows a range of correlation coefficients (r). The orange color represents a positive correlation, decreasing to dark colors bar, which represents a negative correlation
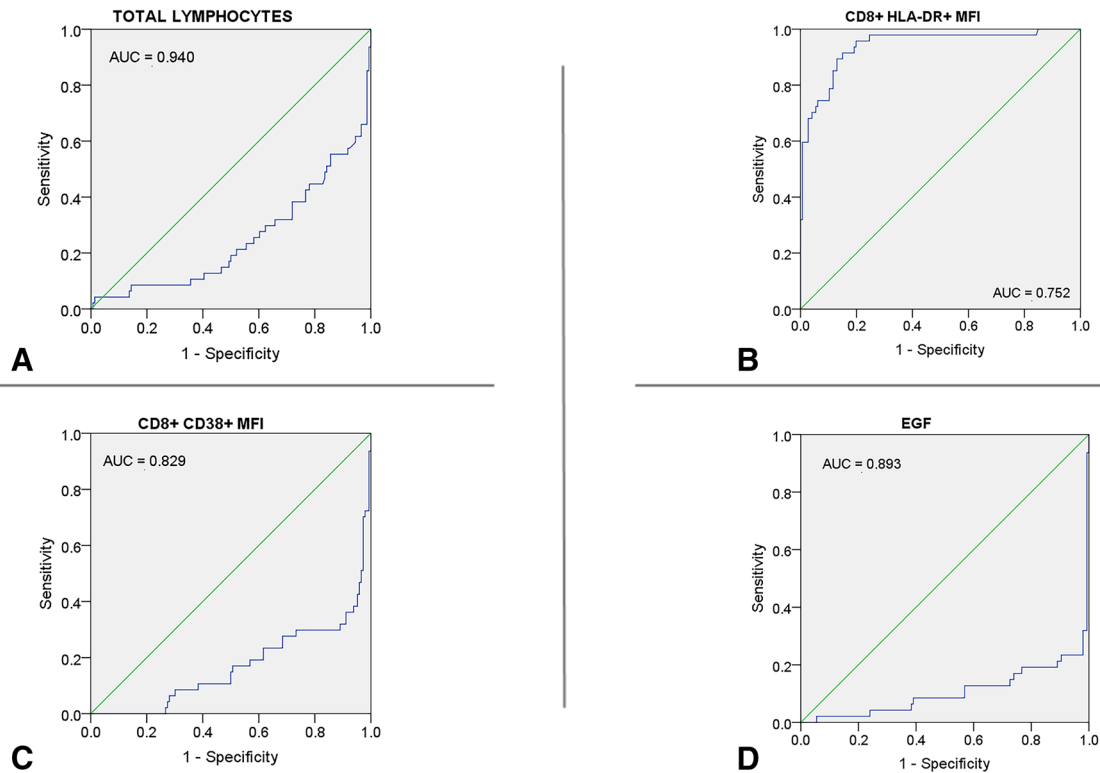

Fig. 4 Receiver operating characteristic curves for immune markers associated with myocardial injury in hypertensive patients with COVID-19. **A**, Total lymphocytes; **B**, CD8+ HLA-DR+ MFI; **C**, CD8+ CD38+ MFI; **D**, EGF. COVID-19, 2019 coronavirus disease; AUC, area under the curve; HLA-DR, human leukocyte antigen DR isotope; MFI, mean fluorescence intensity; EGF, epidermal growth factor

Discussion

Hypertension is among the most common comorbidities associated with worse clinical prognosis in patients with COVID-19 [16]. In this study, we examined the immunological signature of myocardial injury in hypertensive patients with COVID-19 in detail. We found that myocardial injury was associated strongly with immune

Table 2 Univariate and multivariate logistic regression results for the prediction of myocardial injury in hypertensive patients with COVID-19

| Characteristics | Univariate model | | Multivariate model | | |
	OR	p-value	aOR	95% CI	p-value
Sex					
Male	1		1		
Female	0.66	0.268	1.43	0.25—8.21	0.689
Age		<0.001			0.129
28 to 49 years	1		1		
50 to 69 years	3.09	0.053	0.84	0.08—8.36	0.881
70 to 97 years	28.00	<0.001	5.71	0.48—67.3	0.166
Oxygen Saturation					
>93%	1		1		
≤93%	3.63	0.001	3.41	0.53—21.7	0.194
BMI (kg/m^2)		0.004			0.057
≤24,9	1		1		
25 to 29.9	0.58	0.279	9.08	0.73—112.6	0.086
≥30 (obese)	0.19	0.002	1.10	0.06—18.6	0.945
Diabetes					
No	1		1		
Yes	2.82	0.003	6.04	0.97—37.7	0.054
Cardiac comorbidities					
No	1		1		
Yes	5.20	<0.001	5.54	0.66—46.7	0.116
Other comorbidities					
No	1		1		
Yes	8.41	0.001	4.68	0.26—82.9	0.292
HLADR MFI>1790					
No	1		1		
Yes	47.30	<0.001	462.78	37.1—5.771	<0.001
EGF<196					
No	1		1		
Yes	14.16	<0,001	3.56	0.57—22.3	0.175
CD38 MFI<4700					
No	1		1		
Yes	6.69	0.001	35.14	2.66—464.5	0.007
Total lymphocytes<1740					
No	1		1		
Yes	4.65	0.002	39.99	2.51—636.3	0.009

COVID-19, 2019 coronavirus disease; OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval; BMI, body mass index; HLA-DR, human leukocyte antigen DR isotype; MFI, mean fluorescence intensity; EGF, epidermal growth factor

derangement, reflected by differential circulating cytokine levels and immune cellular subset expression and activation. In addition, we identified the CD8$^+$ HLA-DR$^+$ MFI, CD8$^+$ CD38$^+$ MFI, and total lymphocyte count as biomarkers associated with myocardial injury in this population. These data provide new insight on mechanisms of myocardial injury in hypertensive patients with COVID-19.
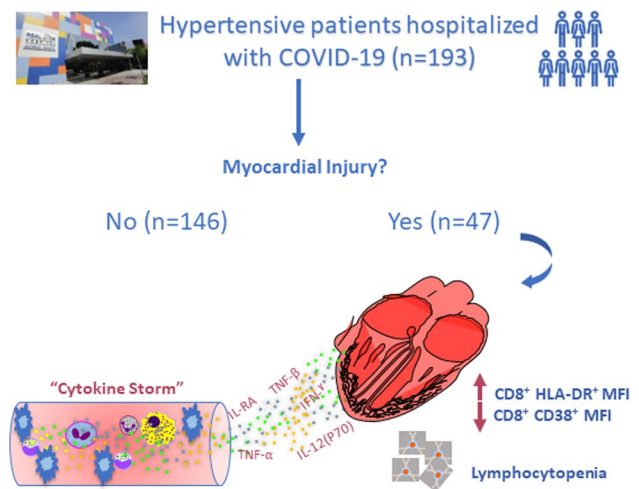
Fig. 5 Schematic illustration of the main findings: immune biomarkers associated with myocardial injury in hypertensive patients hospitalized with COVID-19

Cytokine storms have been associated extensively with COVID-19 progression [12]. In a previous work, we demonstrated the relevance of IL-12 (p70) and IL-10, together with clinical measures obtained at admission, as biomarkers of the increased risk of COVID-19 progression in hypertensive patients [13]. In the present study, the IL-12 (p70) level was higher in hypertensive patients with COVID-19 and myocardial injury than in those without injury, and the IL-10 level showed a clear, albeit non-significant, increasing trend. These findings confirm that these cytokines not only play an important role in disease progression, but also are associated with myocardial injury. The level of IFN-γ, a cytokine classically related to viral infection, was also higher in patients with myocardial injury. IFN-γ elevation is a known independent mortality risk factor in patients with COVID-19 [17]. Although IL-6 and IL-1β elevations have frequently been associated with progression to severe COVID-19 [13, 18, 19], the levels of these cytokines were highly variable in patients with myocardial injury in this study; thus, additional research with larger samples is needed to determine whether these are markers of myocardial injury. Consistent with the characterization of TNF-α as an independent predictor of survival in patients with COVID-19 [20], we observed TNF-α elevation in patients with myocardial injury. Although high circulating levels of EGF have been consistently associated with COVID-19 severity [21, 22], these levels were lower in patients with than in those without myocardial injury in this study, and this variable had a larger effect size than did the other cytokine variables studied. Overall, the data from this study consistently support the hypothesis that cytokines are involved in myocardial injury in hypertensive patients with COVID-19.

Lymphopenia is one of the most important and frequently encountered immune signatures of COVID-19 and progression to severe disease [23, 24]. We found marked lymphopenia, particularly of T lymphocytes, in patients with myocardial injury. We previously proposed lymphopenia as a biomarker of COVID-19 progression risk in hypertensive patients [13, 14] and the present results demonstrate that it is also an important predictor of myocardial injury in these patients. Similarly, immunologic dysregulation with lymphopenia was described in children with multisystem inflammatory syndrome (MIS-C) associated with COVID-19, and the presence of myocardial injury was also reported in these patients [25]. These findings allow us to speculate that the lymphopenia and the cytokine storm play a vital role in the underlying mechanism of myocardial injury in COVID-19 in adults and pediatric patients.

We observed a moderate negative correlation between lymphopenia with IL-10 and IP-10 in patients with no myocardial injury. Lymphopenia and higher levels of both IL-10 and IP-10 have been associated with the severity progression of patients with COVID-19 [26, 27] and, considering that all our patients were hypertensive, it is interesting to remark that a previous study reported higher levels of IP-10 as the strongest independent predictor of increased systolic blood pressure in patients with essential hypertension [28]. In addition, IL-1α was the cytokine that presented the highest number of correlations with the different cell subsets studied in patients with myocardial injury. It is well known that IL-1 has a marked enhancing effect on antigen-specific CD8 + T cell expansion, differentiation, migration to the periphery, and memory [29]. The association between IL-1α and CD8 + T cells activation has also been described in other diseases, like cancer [30]. The higher frequency of correlations observed in patients with myocardial injury compared to patients without myocardial injury reinforces the hypothesis that innate and adaptative immune interplay is involved in the mechanism underlying cardiac injury.

Consistent with the finding that T-lymphocyte activation markers are increased in patients with COVID-19 with worse clinical outcomes [31, 32], we observed a greater percentage of CD8 + CD38 + T cells and greater CD8 + HLA-DR$^+$ MFI in patients with myocardial injury. This T-lymphocyte activation (reflected by CD38$^-$HLA-DR co-expression) is consistent with observed antiviral responses to other infections [21, 33, 34]. Furthermore and similarly, increased percentages of CD8$^+$ CD38$^+$ T lymphocytes predict faster human immunodeficiency virus-1 disease progression and more intensive depletion of CD4$^+$ T lymphocytes in infected patients [35].

Our group previously proposed the CD8$^+$ NKG2A$^+$ MFI at the time of hospital admission, in combination with several clinical variables, as a robust biomarker associated with a high risk of COVID-19 progression in hypertensive patients [14]. In the mentioned study we reported an increase in both CD8 + HLA-DR$^+$ MFI, and CD8$^+$ NKG2A$^+$ MFI on admission, highlighting the dysregulated immune response with increased activation and at the same time exhaustion of cytotoxic T cells. In fact, some studies suggest that exhaustion could be a consequence of the overactivation of CD8 + T cells [36]. This phenomenon of activation and exhaustion concomitantly with immune activation of T cells has been described in other viral infections such as HIV [37].

In addition, our present finding of an inverse relationship between HLADR and CD38 expression has been previously described in HIV infection. Among other studies, Hua et al. (3) have reported that although HIV-specific CD8 + T cells usually express similar levels of two activation markers, they may exhibit a differential expression, with low CD38 and high HLA-DR expression, particularly in HIV-infected patients who exhibit spontaneous viral control. They suggest that this differential CD8 + activation profile is related to a different cytotoxic capacity in HIV-infected patients (3). Together, these findings suggest the presence of diverse CD8 + T cell activation mechanisms that may involve either HLA-DR or CD38, which may be related to different phenotypes.

In the present study, the CD8$^+$ NKG2A$^+$ MFI was greater in patients with myocardial injury, confirming the relevance of this parameter not only for clinical COVID-19 progression but also for myocardial injury. Collectively, the changes observed in several cell subsets studied help to define the immune signature of hypertensive patients with COVID-19 and myocardial injury. The multivariable analysis performed demonstrated the value of lymphopenia, the CD8 + CD38$^+$ MFI, and the CD8$^+$ HLA-DR$^+$ MFI as independent predictors of myocardial injury, even after adjustment for selected clinical and immune markers, highlighting the robustness of our findings.

Regarding the possible role of lymphocytes in the mechanisms underlying myocardial injury, several works have highlighted the presence of non-specific sub-epicardial inflammatory infiltrate in cardiac samples from patients with COVID-19 and myocardial injury [38, 39]. Most of these reports describe atypical cardiac histological patterns, with few cardiac samples fulfilling the classical histological criteria for myocarditis [38]. These findings could be explained by the association of myocardial damage with larger percentages of activated CD8$^+$ T cells, as found in this study. In support to this hypothesis, the essential role of T cells in the mechanisms underlying viral myocarditis has been demonstrated [40]. Additionally, we observed an increase in the level of NKG2A, a marker of T-cell exhaustion, in association with increased T-cell activation, reflecting T-cell dysregulation. Taken together, these data provide a new perspective on the role played by these important immune cells in the main mechanism of myocardial injury in hypertensive patients with COVID-19, offering potential new therapeutic targets.

This study has some limitations. The interval between symptom onset and hospital admission varied among the enrolled patients, although all patients were included in the study in the first week of hospitalization (the median blood collection time interval was 3.0 and 2.0 days after hospitalization for groups with and without myocardial injury, respectively). Other limitation of this study was the lack of data regarding some additional confounding factors such as previous medications or smoking history. In addition, large degrees of variability in a few immune markers together with the presence of some outliers may have reduced the sensitivity of some analyses. However, we log transformed and standardized the immune markers to control for such variability and calculated Cohen's effect sizes to assess the clinical significance of our findings.

Our data reveal immune markers directly involved in the main mechanisms of myocardial injury in hypertensive patients with COVID-19. Based on these findings, we propose lymphopenia, the $CD8^+$ $CD38^+$ MFI, and the $CD8^+$ $HLA-DR^+$ MFI as remarkable immune biomarkers of myocardial injury in this context.

Conclusion

The immune signatures described in the present work may further our understanding of the immune contribution to the mechanisms underlying myocardial injury in hypertensive patients with COVID-19, opening a new avenue for the improvement of the treatment of hypertensive patients with COVID-19 and myocardial injury.

Data Availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

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