INTRAHOSPITAL SUPERVISED EXERCISE TRAINING IMPROVES SURVIVAL RATE AMONG HYPERTENSIVE COVID-19 PATIENTS

**Francisco Fernandez[1,2], **Manuel Vazquez-Muñoz[3], Andrea Canals[4], Alexis Arce-Álvarez[3], Camila Salazar-Ardiles[1,7], Cristian Alvarez[5], Rodrigo Ramirez-Campillo[5], Gregoire P. Millet[6], Mikel Izquierdo[7,8], *David C. Andrade[1]

[1]Exercise Applied Physiology Laboratory, Centro de Investigación en Fisiología y Medicina de Altura, Departamento Biomedico, Facultad de Ciencias de la Salud, Universidad de Antofagasta, Antofagasta, Chile. [2]Programa de Magister en Fisiología Clínica del Ejercicio, Facultad de Ciencias, Universidad Mayor, Santiago, Chile. [3]Escuela de Kinesiología, Facultad de Odontología y Ciencias de la Rehabilitación, Universidad San Sebastián, Santiago, Chile. [4]Unidad de Estadística, Departamento de Calidad, Clínica Santa María, Santiago, Chile. [5]Exercise and Rehabilitation Sciences Laboratory, School of Physical Therapy, Faculty of Rehabilitation Sciences, Universidad Andres Bello, Santiago 7591538, Chile, [6]Institute of Sport Sciences, University of Lausanne, CH-1015, Lausanne, Switzerland, [7]Navarrabiomed, Hospital Universitario de Navarra (HUN), Universidad Pública de Navarra (UPNA), IdiSNA, Pamplona, Spain. [8]CIBER of Frailty and Healthy Aging (CIBERFES), Instituto de Salud Carlos III, Madrid, Spain.

Running Head: intrahospital exercise and COVID-19

** These authors contributed equally to this work.

*Corresponding author: David C. Andrade, Ph.D.
Exercise Applied Physiology Laboratory
Centro de investigación en Fisiología y Medicina de Altura
Departamento Biomedico
Facultad de Ciencias de la Salud,
Universidad de Antofagasta
Antofagasta, Chile.
Tel: +569 88928666
E-mail: dcandrade@uc.cl
david.andrade@uantof.cl

ABSTRACT

Among the people most affected by coronavirus disease 2019 (COVID-19) are those suffering from hypertension (HTN). However, pharmacological therapies for HTN are ineffective against COVID-19 progression and severity. It has been proposed that exercise training (EX) could be used as post-COVID treatment, which does not rule out the possible effects during hospitalization for COVID-19. Therefore, we aimed to determine the impact of supervised EX on HTN patients with COVID-19 during hospitalization. Among a total of 1,508 hospitalized COVID-19 patients (confirmed by PCR), 439 subjects were classified as having HTN and were divided into two groups: EX (n=201) and control (n=238) groups. EX (3 to 4 times per week during all hospitalizations) consisted of aerobic exercises (15 to 45 min) (i.e., walking); breathing exercises (10 to 15 min) (i.e., diaphragmatic breathing, pursed-lip breathing, active abdominal contraction); and musculoskeletal exercises (8–10 sets of 12–15 repetitions/week) (lifting dumbbells, standing up and sitting, lumbar stabilization). Our data revealed that the EX (clinician: patient, 1:1 ratio) intervention was able to improve survival rates among controlled HTN patients with COVID-19 during their hospitalization when compared to the control group (chi-squared: 4.83; hazard ratio: 1.8; 95% CI: 1.117 to 2.899; p=0.027). Multivariate logistic regression analysis revealed that EX was a prognostic marker (odds ratio: 0.449; 95% CI: 0.230 to 0.874; p=0.018) along with sex and invasive and non-invasive mechanical ventilation. Our data showed that an intrahospital supervised EX program reduced the mortality rate among HTN patients suffering from COVID-19 during their hospitalization.

New & Noteworthy

In the present study, we found that exercise training improves the survival rate in hypertensive COVID-19 patients during their hospitalization period. Our results provide strong evidence for the therapeutic efficacy of exercise training as a feasible approach to improving the outcomes of COVID-19 patients who suffer from hypertension during their hospitalization.

Keywords: COVID-19, hypertension, exercise training, intrahospital.

INTRODUCTION

The current coronavirus disease-2019 (COVID-19) pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1, 2). Several risk factors affect the severity and prognosis of COVID-19, which promote the adoption of individualized adaptation of personalized treatment, prevention, and focused nursing (3). Case series and retrospective cohort studies initially explored the associations of epidemiological and comorbidity factors with the severity and prognosis of COVID-19 (4). The health comorbidities of most concerns among COVID-19 patients are obesity, diabetes, and hypertension (HTN), which are highly prevalent in Latin America and the Caribbean (5-7). Indeed, it has been reported that the prevalence of HTN is 20.9, 16.0, and 14.5% in Mexico, Chile, and Argentina, respectively (8).

Among the patients most affected by COVID-19 are those who suffer from HTN, and it has been shown that HTN could increase mortality risk among COVID-19 patients (9, 10). In addition, older people >60 years of age suffer some degree of HTN, and the British Heart Foundation and the Health Service Executive in Ireland have declared these patients "at risk" of suffering the more severe consequences of COVID-19 (11, 12). Although there are effective pharmacological therapies for HTN, these are ineffective against COVID-19, even though most people who receive them are elderly individuals who suffer from HTN (11, 13)

One of the more critical nonpharmacological treatments against several pathophysiological conditions is exercise training (EX) (14). A recent meta-analytic review of data from 1,853,610 adults shows that individuals who engage in regular physical activity (i.e., by achieving at least 500 MET-min/week of physical activity) have a lower likelihood of SARS-CoV-2 infection, COVID-19 hospitalization, severe COVID-19 illness, and COVID-19-related death than physically inactive individuals, independent of design and instrument used (15). It has been also proposed that EX could be utilized as post-COVID treatment, which does not rule out the plausible positive effects during COVID-19 hospitalization (16, 17). However, the possible impact of an intrahospital supervised EX intervention on the survival rate of HTN patients has not yet been described. Therefore, we aimed to determine the effects of supervised EX on HTN patients with COVID-19 during their hospitalization.

METHODS

Study Population

We retrospectively (ethical approval #550211-20) assessed the effects of an intrahospital supervised EX program for controlled HTN patients with COVID-19 (confirmed by positive PCR) on the probability of survival during hospitalization. Among 1,508 hospitalized COVID-19 patients, 439 subjects were classified as having HTN and divided into two groups: EX (n=201) and control (n=238) groups. All patients were classified as having severe illnesses. The degree of severity was defined based on the 3M™ International Refined Diagnosis-Related Group system (IR-DRGs). Of note, during the development of this study, no patient was vaccinated against COVID-19.

Exercise training Protocol

The EX protocol **(Table 1)** was based on the recommendations of the proposed cardiac rehabilitation protocol (16). EX started when patients were stabilized considering the following parameters at rest: fraction of inspired O_2 ≤60%; O_2 saturation ≥90%; respiratory frequency ≤40 breaths/min; positive end-expiratory pressure ≤10 cmH_2O; systolic blood pressure (BP) ≥90 and ≤195 mmHg; mean arterial BP ≥65 and ≤110 mmHg; heart rate ≥40 and ≤120 beats/min; body temperature ≤38.5 °C; Richmond Agitation-Sedation Scale score from -2 to 2; intracranial pressure <20 cmH_2O; and venous blood lactate <4 mmol/L. In addition, patients with arrhythmias, myocardial ischaemia, venous thrombosis, pulmonary embolism, aortic constriction, or renal disease were excluded.

*****Table 1 near here*****

Anthropometrics

Before exercise training, all patients were subjected to anthropometric and cardiorespiratory assessments. Body weight was estimated to the nearest 0.1 kg using a digital scale (BF-350, Tanita, IL, USA). Body height was measured using a wall-mounted stadiometer (HR-200, Tanita, Japan) and recorded to the nearest 0.1 cm. Body mass index (BMI) was calculated as body weight/body height^2 (kg/m^2). In addition, the participants were instrumented and positioned in the supine position, and core temperature, oxygen saturation using a pulse oximeter placed on the index finger or the thumb (SpO_2) (BK-PO2, BiOBASE, China), and respiratory frequency (R_f) were measured.

Blood pressure measurement

Systolic and diastolic blood pressure (SBP and DBP, respectively) were assessed at baseline before the EX-intervention. From the SBP and DBP, we calculated the mean arterial blood pressure (MABP) (1/3 of SBP + 2/3 of DBP) and pulse pressure (PP) (SBP-DBP). Blood pressure (BP) and heart rate (HR) were determined using an automated blood pressure monitor (Omron® HEM 7114, Omron Healthcare Inc., Lake Forest, IL, USA). Readings were taken from the left arm in triplicate (2-minute intervals between measurements) and after 15 minutes of rest with the subjects seated.

Medications

The medication information of each patient was obtained from the medical folders. The most commonly used medications among the patients were i) thiazide diuretics; ii) calcium antagonists; iii) angiotensin-converting enzyme (ACE) inhibitors; iv) angiotensin receptor blockers (ARBs); v) beta-adrenergic blocking agents (**Table 2**). Of note, there were significant differences in the consumption of beta-adrenergic blockers.

*****Table 2 near here*****

Data Analysis

Data are shown as mean ± standard deviations (SDs) or min-max. The survival data were analyzed by the log-rank Cox test and a multivariate logistic regression model. The alpha value was set to $p<0.05$. Analysis was performed with GraphPad Prism 9.2 (USA, La Jolla, CA).

RESULTS

Prior to the EX-training intervention, we did not observe significant differences in age, temperature, body weight, body height, BMI, R_f, SpO_2, SBP, DBP, PP, MABP, or HR (all $p > 0.05$) between groups (**Table 3**).

*****Table 3 near here*****

Importantly, our data revealed that an intrahospital supervised (clinician: patient, 1:1 ratio) cardiovascular rehabilitation EX intervention was able to improve the probability of survival among controlled HTN patients with COVID-19 during their hospitalization when compared to the control group (chi-squared: 4.83; hazard ratio: 1.8; 95% CI: 1.117 to 2.899; p=0.027) (**Figure 1**). In addition, EX was able to reduce lethality among HTN patients suffering from COVID-19 (EX, survival: 185 [92.03%]; deaths: 16 [7.96%] vs. control, survival: 176 [73.94%]; deaths: 62 [26.05%]). Multivariate logistic regression analysis revealed that EX was a prognostic marker (odds ratio: 0.448; 95% CI: 0.230 to 0.873; p=0.018) along with sex (odds ratio: 3.121; 95% CI: 1.576 to 6.178; p=0.001), non-invasive mechanical ventilation (NIMV, odds ratio: 5.964; 95% CI: 3.093 to 11.497; p<0.001) and extracorporeal membrane oxygenation (ECMO, odds ratio: 0.055; 95% CI: 0.024 to 0.125; p<0.001) (**Table 4**).

*****Figure 1 near here*****

Table 4 near here

DISCUSSION

The main finding of the present study was that an intrahospital supervised exercise training intervention was able to promote an improvement in the survival rate of HTN patients with COVID-19 during their hospitalization. Our data suggest that an intrahospital supervised EX program is a feasible approach to improve the outcomes of COVID-19 patients who suffer from hypertension during their hospitalization.

COVID-19 and chronic diseases

Most COVID-19 patients admitted to the intensive care unit (ICU) suffer from several comorbidities, which are risk factors for hospitalization (18). Being overweight and obesity are related to decreased oxygen saturation resulting from reduced ventilation at the base of the lungs. Notably, it is estimated that 47.6% of obese patients are infected with COVID-19, and 68.6% are ventilated because they are critically ill (19). Our data indicate that COVID-19 patients with HTN display a similar body weight and body mass index (~28 kg/m^2), which is classified as overweight. Accordingly, it is possible to speculate that this morphological characteristic partially explains our participants' ICU hospitalization.

Hypertension (HTN) and COVID-19

Hypertension is the leading cause of premature death worldwide and is associated with an estimated global medical cost of $370 billion per year (20). The American

College of Cardiology, in conjunction with the American Heart Association in 2017, proposed a BP ≥ 130/80 mm Hg as a new threshold for the diagnosis of hypertension (21). Given the high prevalence of HTN and its negative health consequences, strategies other than pharmacological treatment become necessary for managing this condition. For this reason, nonpharmacological interventions aimed at lifestyle changes, mainly physical exercise, are of fundamental importance (22).

HTN is strongly associated with COVID-19 infection and mortality rates (23, 24). One of the first-line drugs that are frequently used to treat HTN is ACE-2 inhibitors and angiotensin receptor blockers (ARBs). Paradoxically, chronic administration of ACE-2 inhibitors positively regulates ACE-2 receptor expression, leading to increased susceptibility to contracting SARS-CoV-2 in HTN patients (25). Increased expression of ACE-2 receptors at the pulmonary level leads to increased infection susceptibility, increasing the risk of severe lung injury and respiratory failure during COVID-19 (25). The participants in our study used ARBs as a treatment for HTN, which could explain, in part, the severity of the pathophysiological state promoted by COVID-19 in these participants with HTN. Accordingly, the Department of Epidemiology of China showed that HTN was the most frequent comorbidity among COVID-19 patients (12.8%). Notably, the overall mortality rate was 2.3%, and the most affected were those older than 80 years (14.8%). Mortality by sex was 2.8% for men and 1.7% for women (26). In our study, we observed that sex was a prognostic marker for mortality, which could be explained by the fact that the combination of aerobic exercise and muscular strength improves fat-free mass in men more than women (36). Our data indicate that the lethality was 26.05% among COVID-19 patients with HTN, which was markedly improved by the exercise training intervention (7.96%), suggesting that EX could be a feasible treatment approach for COVID-19+HTN patients. All the evidence demonstrates that HTN is one of the most recurrent comorbidities and has the most substantial negative implications during COVID-19 infection, suggesting that it is necessary to seek alternatives, such as exercise training, for the treatment and follow-up of COVID-19 patients with HTN at baseline.

COVID-19, hypertension, and exercise

It has been shown that aerobic physical exercise positively impacts BP levels and should be one of the fundamental pillars of a training program for patients with HTN (27). International recommendations support engaging in 150-300 minutes of moderate-vigorous physical activity per week plus two days of muscular resistance training. Among the primary modalities with proven benefits in reducing BP are aerobic exercises, muscular strength exercises, and isometric exercises (28,29,41,42). Mechanistically, nitric oxide-dependent exercise training has been proposed as one of the more essential adaptations following an exercise training period. It has been demonstrated that after one bout of exercise, an improvement in vascular function was observed 1 to 24 hours post-exercise, which persisted 24 to 48 hours post-exercise training (43, 44). Notably, the improvement of vascular function after regular exercise is the protection against increases in BP in hypertension patients (43, 44). In addition, another mechanism related to BP reduction following exercise training is the decreased sympathetic drive, evidenced by reduced plasma norepinephrine and renin activity, as well as decreased renal and muscular sympathetic activity (45, 46, 47).

Regarding exercise intensity, Lopes et al. 2020, compared differences between low training intensity (<30% FCR) vs. moderate intensity (60% FCR), concluding that both training intensities generate benefits on BP control (39). Previously, Eicher et al. (2010) demonstrated that a single physical exercise session was able to reduce BP levels independently of the intensity (low, moderate, and vigorous) (40). Therefore, the training performed by the subjects during hospitalization could have beneficial effects on BP even if they were performed at very low intensity. Thus, our results demonstrate that low-intensity exercise could impact not only the cardiovascular system but also the mortality rate in COVID-19 patients suffering from hypertension.

A recent series of systematic reviews demonstrated the need for early rehabilitation of COVID-19 patients admitted in the recovery phase after severe respiratory failure due to COVID-19 (30). Compared with patients with mild sequelae resulting from COVID-19, neuromotor rehabilitation, home rehabilitation, and telerehabilitation are recommended, in addition to light sports activities such as yoga and tai chi (31). For outpatient management of mild infections, pulmonary rehabilitation, education, airway clearance techniques, physical exercise, breathing exercises, and others can be considered (32). Light activities such as yoga and tai chi that coordinate postural movements with breathing have been recommended (33). Our results showed that an EX-intervention markedly improved the mortality rate among COVID-19 patients with HTN, suggesting that light exercise could be considered a first-line treatment for COVID-19 patients suffering from HTN.

In the management of acutely hospitalized patients, physical exercise is recommended as a fundamental component in pulmonary rehabilitation; it should begin with bed mobility for very deconditioned patients and ramp up to walking for ambulatory patients, in addition to considering respiratory exercises to increase thoracic expansion, improve diaphragmatic incursion and techniques for bronchial cleansing (34). The goal of rehabilitation should be to obtain an oxygen saturation (SpO_2) above 90% with supplemental oxygen to maintain the target SpO_2 (34). Of note, our EX-intervention considered several variables to preserve the stability of the patients.

Exercise and Immune Function

Exercise-focused therapies could help to improve the immune system by reducing oxidative stress related to pro-inflammatory markers as well as enhancing the body's immune response to a viral or bacterial agent. The called "cytokine storm" is a common term used to describe the extreme and complex inflammatory response to a viral infection that also could occur during SARS-CoV2 infection. The inflammatory response is disproportionate, resulting in hypercytokinemia triggering acute respiratory distress syndrome (ARDS), and in the worst cases, death (37). It is assumed that elevated cytokine levels could increase blood viscosity, further increasing the possibility of thromboembolism or vascular coagulation (38). We could interpret that our results could be partly explained by the reduction of low-grade systemic inflammation, together with a reduction of the "cytokine storm," which would result in a reduction of mortality in the experimental group.

Limitations

The study has limitations due to its retrospective design, and the inclusion of subjects in the training protocol depended exclusively on the criteria of the physician on duty, which increases the risk of bias in the intervention. However, the physician on duty evaluated the following parameters for patient inclusion: oxygen saturation, systolic blood pressure, and symptomatology. In addition, there was no follow-up after discharge from the intensive care unit to home. In addition, our patients displayed a pharmacological heterogeneity, which could affect our results. In fact, we observed a significant difference between groups regarding beta-adrenergic blocking agents, which have promoted adverse effects in COVID-19 patients (48, 49). Thus, our results did not discard the possible role of the pharmacological profile on the patient's outcome.

CONCLUSIONS

Our data suggest that physical exercise is a feasible approach to increase the probability of survival of HTN patients with COVID-19 during hospitalization. However, the study results raise questions that should be investigated in the future, such as the mechanisms inherent to physical exercise, which are directly related to reducing mortality. As a practical application, the exercise protocol used in this study may be helpful in the clinical management of COVID-19 patients in the ICU. This study represents an advance in the treatment of COVID-19; however, it is recommended that in future research, different exercise modalities be linked during hospitalization as a result of COVID-19 to evaluate the effectiveness of different types of exercises. Further research in this area is recommended, which could benefit this target population in the medium and long term.

FUNDING

This study was supported by Minera Escondida Ltda. MEL2203; the “Agencia Nacional de Investigación y Desarrollo (ANID)”, through Fondecyt de Iniciación #11220870 and Anillo ACT210083.

CONFLICT OF INTEREST

None.

ACKNOWLEDGEMENT

Authors thanks to the Minera Escondida Ltda. MI was funded in part by grant from the Spanish Ministry of Economy, “Ministerio de Ciencia e Innovación” (PID2020-113098RB-I00)

AUTHOR CONTRIBUTION

F.F., and M.V-M., contributed to the draft and preparation of the manuscript. F.F., M.V-M., and A.C., contributed to the analysis of the data. A.A.A., C.S-A., C.A., R-R-C., G.P-M., and M.I., contributed to the preparation of the manuscript. D.C.A. contributed to the concept of the project. D.C.A. contributed to the preparation of the manuscript. All authors approved the final version of the manuscript.

REFERENCES

1. **Baloch S, Baloch MA, Zheng T, and Pei X**. The Coronavirus Disease 2019 (COVID-19) Pandemic. *Tohoku J Exp Med* 250: 271-278, 2020.

2. **Candido KL, Eich CR, de Farina LO, Kadowaki MK, da Conceicao Silva JL, Maller A, and Simao RCG**. Spike protein of SARS-CoV-2 variants: a brief review and practical implications. *Braz J Microbiol* 53: 1133-1157, 2022.

3. **Fang L, Karakiulakis G, and Roth M**. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med* 8: e21, 2020.

4. **Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, and Cao B**. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 395: 497-506, 2020.

5. **Ceriello A, and Schnell O**. COVID-19: Considerations of Diabetes and Cardiovascular Disease Management. *J Diabetes Sci Technol* 14: 723-724, 2020.

6. **Kumar A, Arora A, Sharma P, Anikhindi SA, Bansal N, Singla V, Khare S, and Srivastava A**. Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. *Diabetes Metab Syndr* 14: 535-545, 2020.

7. **Prattichizzo F, Bonafè M, Giuliani A, Costantini A, Storci G, Sabbatinelli J, and Olivieri F**. Response to: Letter to the Editor on "Bonafè M, Prattichizzo F, Giuliani A, Storci G, Sabbatinelli J, Olivieri F. Inflamm-aging: Why older men are the most susceptible to SARS-CoV-2 complicated outcomes. Cytokine Growth Factor Rev" by Eugenia Quiros-Roldan, Giorgio Biasiotto and Isabella Zanella. *Cytokine Growth Factor Rev* 58: 141-143, 2021.

8. **Anaya-Covarrubias JY, Pizuorno A, Mirazo S, Torres-Flores J, Du Pont G, Lamoyi E, and Fierro NA**. COVID-19 in Latin America and the caribbean region: Symptoms and morbidities in the epidemiology of infection. *Curr Opin Pharmacol* 63: 102203, 2022.

9. **Nemunaitis JJ, and Stanbery L**. Faculty Opinions recommendation of Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Faculty Opinions – Post-Publication Peer Review of the Biomedical Literature* 2020.

10. **Yang Q, Zhou Y, Wang X, Gao S, Xiao Y, Zhang W, Hu Y, and Wang Y**. Effect of hypertension on outcomes of adult inpatients with COVID-19 in Wuhan, China: a propensity score-matching analysis. *Respir Res* 21: 172, 2020.

11. **Clark CE, McDonagh STJ, McManus RJ, and Martin U**. COVID-19 and hypertension: risks and management. A scientific statement on behalf of the British and Irish Hypertension Society. *J Hum Hypertens* 35: 304-307, 2021.

12. **Khan NA, Stergiou GS, Omboni S, Kario K, Renna N, Chapman N, McManus RJ, Williams B, Parati G, Konradi A, Islam SM, Itoh H, Mooi CS, Green BB, Cho M-C, and Tomaszewski M**. Virtual management of hypertension: lessons from the COVID-19 pandemic–International Society of Hypertension position paper endorsed by the World Hypertension League and European Society of Hypertension. *Journal of Hypertension* 40: 2022.

13. **Sanders JM, Monogue ML, Jodlowski TZ, and Cutrell JB**. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. *JAMA* 323: 1824-1836, 2020.

14. **Odusanya OO, Odugbemi BA, Odugbemi TO, and Ajisegiri WS**. COVID-19: A review of the effectiveness of non-pharmacological interventions. *Niger Postgrad Med J* 27: 261-267, 2020.

15. **Ezzatvar Y, Ramirez-Velez R, Izquierdo M, and Garcia-Hermoso A**. Physical activity and risk of infection, severity and mortality of COVID-19: a systematic review and non-linear dose-response meta-analysis of data from 1 853 610 adults. *Br J Sports Med* 2022.

16. **Calabrese M, Garofano M, Palumbo R, Di Pietro P, Izzo C, Damato A, Venturini E, Iesu S, Virtuoso N, Strianese A, Ciccarelli M, Galasso G, and Vecchione C**. Exercise Training and Cardiac Rehabilitation in COVID-19 Patients with Cardiovascular Complications: State of Art. *Life (Basel)* 11: 2021.

17. **Kato M, Ono S, Seko H, Tsukamoto T, Kurita Y, Kubo A, Omote T, and Omote S**. Trajectories of frailty, physical function, and physical activity levels in elderly patients with heart failure: impacts of interruption and resumption of outpatient cardiac rehabilitation due to COVID-19. *International Journal of Rehabilitation Research* 44: 200-204, 2021.

18. **Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, and Peng Z**. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *Jama* 323: 1061-1069, 2020.

19. **World Health O**. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance, 13 March 2020 Geneva: World Health Organization, 2020.

20. **Frieden TR, and Jaffe MG**. Saving 100 million lives by improving global treatment of hypertension and reducing cardiovascular disease risk factors. *J Clin Hypertens (Greenwich)* 20: 208-211, 2018.

21. **Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC, Jr., Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA, Sr., Williamson JD, and Wright JT, Jr.** 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 71: 1269-1324, 2018.

22. **Saco-Ledo G, Valenzuela PL, Ruiz-Hurtado G, Ruilope LM, and Lucia A**. Exercise Reduces Ambulatory Blood Pressure in Patients With Hypertension: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Am Heart Assoc* 9: e018487, 2020.

23. **Ejaz H, Alsrhani A, Zafar A, Javed H, Junaid K, Abdalla AE, Abosalif KOA, Ahmed Z, and Younas S**. COVID-19 and comorbidities: Deleterious impact on infected patients. *J Infect Public Health* 13: 1833-1839, 2020.

24. **Martini N, Piccinni C, Pedrini A, and Maggioni A**. [CoViD-19 and chronic diseases: current knowledge, future steps and the MaCroScopio project.]. *Recenti Prog Med* 111: 198-201, 2020.

25. **Fang X, Li S, Yu H, Wang P, Zhang Y, Chen Z, Li Y, Cheng L, Li W, Jia H, and Ma X**. Epidemiological, comorbidity factors with severity and prognosis of COVID-19: a systematic review and meta-analysis. *Aging (Albany NY)* 12: 12493-12503, 2020.

26. [The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China]. *Zhonghua Liu Xing Bing Xue Za Zhi* 41: 145-151, 2020.

27. **Pescatello LS, MacDonald HV, Lamberti L, and Johnson BT**. Exercise for Hypertension: A Prescription Update Integrating Existing Recommendations with Emerging Research. *Curr Hypertens Rep* 17: 87, 2015.

28. **Sharman JE, La Gerche A, and Coombes JS**. Exercise and cardiovascular risk in patients with hypertension. *Am J Hypertens* 28: 147-158, 2015.

29. **Weston KS, Wisløff U, and Coombes JS**. High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis. *Br J Sports Med* 48: 1227-1234, 2014.

30. **Negrini S, Mills JA, Arienti C, Kiekens C, and Cieza A**. "Rehabilitation Research Framework for Patients With COVID-19" Defined by Cochrane Rehabilitation and the World Health Organization Rehabilitation Programme. *Arch Phys Med Rehabil* 102: 1424-1430, 2021.

31. **de Sire A, Andrenelli E, Negrini F, Negrini S, and Ceravolo MG**. Systematic rapid living review on rehabilitation needs due to COVID-19: update as of April 30th, 2020. *Eur J Phys Rehabil Med* 56: 354-360, 2020.

32. **Zhao HM, Xie YX, and Wang C**. Recommendations for respiratory rehabilitation in adults with coronavirus disease 2019. *Chin Med J (Engl)* 133: 1595-1602, 2020.

33. **Ngai SP, Jones AY, and Tam WW**. Tai Chi for chronic obstructive pulmonary disease (COPD). *Cochrane Database Syst Rev* 2016: Cd009953, 2016.

34. **Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, Hill K, Holland AE, Lareau SC, Man WD, Pitta F, Sewell L, Raskin J, Bourbeau J, Crouch R, Franssen FM, Casaburi R, Vercoulen JH, Vogiatzis I, Gosselink R, Clini EM, Effing TW, Maltais F, van der Palen J, Troosters T, Janssen DJ, Collins E, Garcia-Aymerich J, Brooks D, Fahy BF, Puhan MA, Hoogendoorn M, Garrod R, Schols AM, Carlin B, Benzo R, Meek P, Morgan M, Rutten-van Mölken MP, Ries AL, Make B, Goldstein RS, Dowson CA, Brozek JL, Donner CF, and Wouters EF**. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med* 188: e13-64, 2013.

35. **Wang TJ, Chau B, Lui M, Lam GT, Lin N, and Humbert S**. Physical Medicine and Rehabilitation and Pulmonary Rehabilitation for COVID-19. *Am J Phys Med Rehabil* 99: 769-774, 2020.

36. **Donges CE, Duffield R.** Effects of resistance or aerobic exercise training on total and regional body composition in sedentary overweight middle-aged adults. *Appl Physiol Nut Metabol.* 2012;37:499–509. doi: 10.1139/h2012-006.

37. **Jose RJ, Manuel A.** COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir Med.* 2020; 8:e46–e47. doi: 10.1016/S2213-2600(20)30216-2.

38. **Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S**. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. *Clin Rheumatol.* 2020; 39:2085–2094. doi: 10.1007/s10067-020-05190-5.

39. **Lopes J, Fonseca M, Torres-Costoso A, López-Muñoz P, Alves AJ, Magalhães P, Ribeiro F**. Low- and moderate-intensity aerobic exercise acutely reduce blood pressure in adults with high-normal/grade I hypertension. J Clin Hypertens (Greenwich). 2020 Sep;22(9):1732-1736. doi: 10.1111/jch.14000. Epub 2020 Aug 9. PMID: 33460204; PMCID: PMC8029894.

40. **Eicher, J. D., Maresh, C. M., Tsongalis, G. J., Thompson, P. D., & Pescatello, L. S.** (2010). The additive blood pressure lowering effects of exercise intensity on post-exercise hypotension. *American heart journal*, *160*(3), 513–520. https://doi.org/10.1016/j.ahj.2010.06.005

41. **Radak, Z., Chung, H. Y., Koltai, E., Taylor, A. W., & Goto, S.** (2008). Exercise, oxidative stress and hormesis. In Ageing Research Reviews (Vol. 7, Issue 1, pp. 34–42). https://doi.org/10.1016/j.arr.2007.04.004

42. **Radak, Z., Ihasz, F., Koltai, E., Goto, S., Taylor, A. W., & Boldogh, I.** (2014). The redox-associated adaptive response of brain to physical exercise. In Free Radical Research (Vol. 48, Issue 1, pp. 84–92). https://doi.org/10.3109/10715762.2013.826352.

43. **Dawson, E. A., Green, D. J., Timothy Cable, N., & Thijssen, D. H. J.** (2013). Effects of acute exercise on flow-mediated dilatation in healthy humans. In Journal of Applied Physiology (Vol. 115, Issue 11, pp. 1589–1598). https://doi.org/10.1152/japplphysiol.00450.2013
44. **Hwang, I.-C., Kim, K.-H., Choi, W.-S., Kim, H.-J., Im, M.-S., Kim, Y.-J., Kim, S.-H., Kim, M.-A., Sohn, D.-W., & Zo, J.-H.** (2012). Impact of acute exercise on brachial artery flow-mediated dilatation in young healthy people. In Cardiovascular Ultrasound (Vol. 10, Issue 1). https://doi.org/10.1186/1476-7120-10-39.
45. **Barochiner, J., Martínez, R., & Aparicio, L. S.** (2021). Novel Indices of Home Blood Pressure Variability and Hypertension-Mediated Organ Damage in Treated Hypertensive Patients. In High Blood Pressure & Cardiovascular Prevention. https://doi.org/10.1007/s40292-021-00453-x.
46. **Fagard, R. H., & Cornelissen, V. A.** (2007). Effect of exercise on blood pressure control in hypertensive patients. In European Journal of Cardiovascular Prevention & Rehabilitation (Vol. 14, Issue 1, pp. 12–17). https://doi.org/10.1097/hjr.0b013e3280128bbb.
47. **Inc., K. N., & Kernel Networks Inc.** (2019). Acute Effect of Isometric Exercise on Blood Pressure in Hypertensive Patients. In Case Medical Research. https://doi.org/10.31525/ct1-nct03982758.
48. **Li, M., Wang, Y., Ndiwane, N., Orner, M. B., Palacios, N., Mittler, B., Berlowitz, D., Kazis, L. E., & Xia, W.** (2021). The association of COVID-19 occurrence and severity with the use of angiotensin converting enzyme inhibitors or angiotensin-II receptor blockers in patients with hypertension. PloS One, 16(3), e0248652.
49. **Ma, Y., Zhang, Y., Li, S., Yang, H., Li, H., Cao, Z., Xu, F., Sun, L., & Wang, Y.** (2021). Sex Differences in Association Between Anti-Hypertensive Medications and Risk of COVID-19 in Middle-Aged and Older Adults. Drugs & Aging, 38(10), 921–930.

FIGURE LEGEND

Figure 1. Intrahospital exercise training increases the probability of survival in hypertensive COVID-19 patients. Of note, the EX was able to promote a significant reduction in the probability of survival in HTN patients suffering from COVID-19 during their hospitalization. Log-rank Cox test, Chi-squared: 4.83; Hazard ratio: 1.8; 95% CI: 1.117 to 2.899; p=0.027.

INTRAHOSPITAL SUPERVISED EXERCISE TRAINING IMPROVES SURVIVAL RATE AMONG HYPERTENSIVE COVID-19 PATIENTS

METHODS

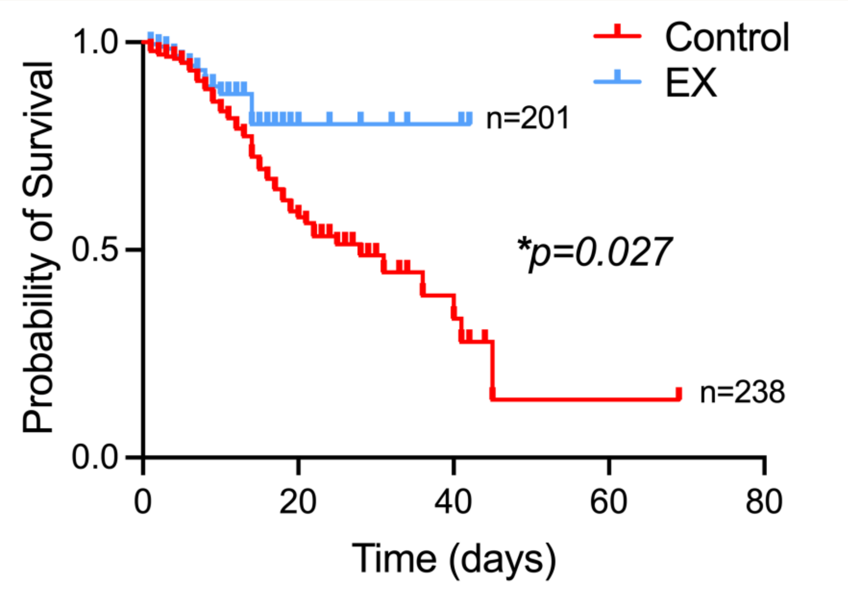
COVID-19 patients
(n=1,508)

Hypertension
(n=439)

Sedentary
(n=238)

Exercise training
(n=201)

OUTCOME Mortality



CONCLUSION low-intensity exercise training improves survival rate in COVID-19 hypertensive patients.

doi here

TABLES

Table 1. Exercise training (EX) intervention characteristics.

	Modality	Volume	Intensity	Frequency
Cardiopulmonary	Aerobic exercises (walk, walk in eight, military march, and walk on tiptoe and heels)	10-15 minutes for the first 3-4 sessions and incrementally increase. 15-45 min each session	Borg dyspnea score ≤ 4; scale for fatigue (must not exceed a score of 11–12)	1-2 times per day, 3-4 times a week
Breathing exercises	Diaphragmatic breathing, Pursed lip breathing, Active abdominal contraction	2-3 times/day, daily: 10-15 minutes for the first 3-4 sessions	Borg dyspnea score ≤ 4; scale for fatigue (must not exceed a score of 11–12)	1-2 times per day, 3-4 times a week
Musculoskeletal	Musculoskeletal (Lifting dumbbells, standing up and sitting, lumbar stabilization)	Resistance exercises	8–10 sets of 12–15 repetitions/week	1-2 times per day, 3-4 times a week

The following parameters were constantly evaluated during EX:

Saturation: must remain above 92–93% during the whole exercise.

Heart rate: must not increase more than 20 beats per minute from the baseline heart rate during mild intensity exercise (patient's pharmacological therapy should also be carefully considered, especially the use of beta-blockers that limit the physiological increase in frequency during exercise).

Systolic blood pressure: must be ≥90 mmHg and ≤195 mmHg,

Symptomatology: with the use of the Borg scale for dyspnea (must not exceed a score of 4) and of the rate of perceived exertion (RPE) scale for fatigue (must not exceed a score of 11–12).

The exercise training protocol was based on previous recommendations (35).

Table 2 Hypertensive medication profile.

	HTN N = 238	HTN+EX N= 201	p-value
Thiazide Diuretics	n = 67 (28.15%)	n = 26 (12.93%)	**0.007**
Calcium Antagonist	n = 57 (23.94%)	n = 35 (17.41%)	0.236
Angiotensin Converting enzyme (ACE)	n = 27 (11.34%)	n = 18 (8.95%)	0.617
Angiotensin receptor Blockers (ARBs)	n = 92 (38.65%)	n = 64 (31.84%)	0.439
Beta-Adrenergic Blocking Agents	n = 51 (21,42%)	n = 15 (7.46%)	**0.002**
No medication reported	n = 2 (0.84%)	n = 0 (0.00%)	0.215

Data are shown as the number of subjects (n) and % of total patients. The medication was classified accordingly to its action mechanism. Data were analyzed using Mann-Whitney non-parametric test. A $p<0.05$ was considered significant.

Table 3. Pre-exercise resting parameters.

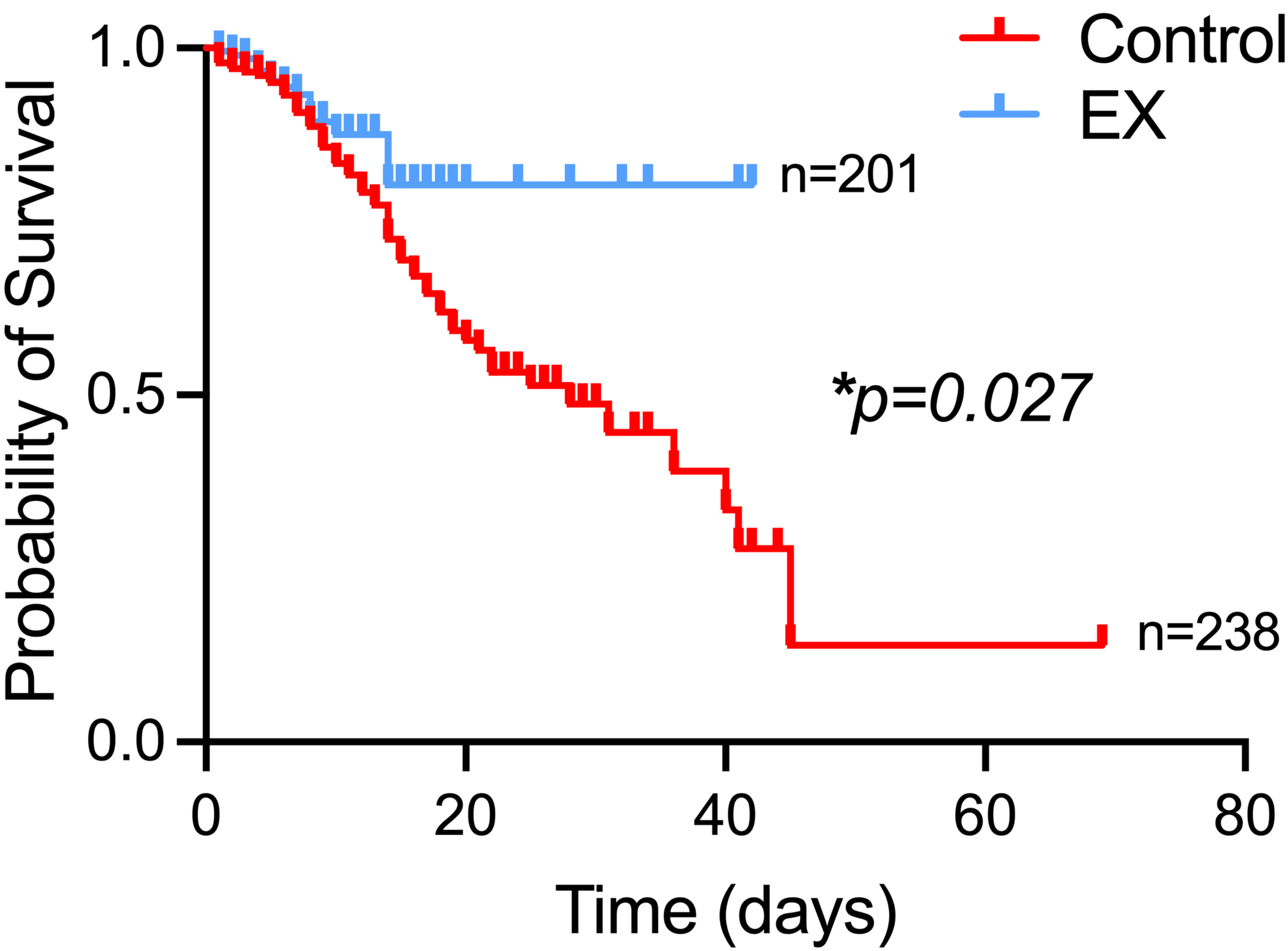
	HTN n=238		HTN+EX n=201		
	F, n=94 (40%)/M, n=144 (60%)		F, n=99 (49%)/M, n=102 (51%)		
	Mean ± SD	Min-max	Mean ± SD	Min-max	p-value
Age (y)	66.22 ± 14.10	24 – 96	64.18 ± 14.32	28 – 99	0.963
Temperature (°C)	36.70 ± 0.79	35 – 39	36.73 ± 0.73	35 – 40	0.751
Body weight (kg)	80.70 ± 15.39	46 – 118	77.50 ± 11.10	55 – 100	0.507
Body height (cm)	167.20 ± 9.17	148 – 184	164.10 ± 9.77	150 – 180	0.316
BMI (kg/m^2)	28.81 ± 5.60	18 – 42	28.71 ± 3.90	21 – 33	0.991
R_f (breaths/min)	24.33 ± 7.53	10 – 59	23.45 ± 6.53	7 – 69	0.210
SpO2 (%)	93.68 ± 7.54	50 – 100	94.74 ± 4.80	65 – 100	0.091
SBP (mmHg)	141.10 ± 26.00	85 – 195	143.51 ± 22.80	103 – 190	0.541
DBP (mmHg)	75.51 ± 14.70	44 – 115	76.60 ± 10.81	58 – 105	0.605
PP (mmHg)	60.01 ± 22.10	16 – 140	58.40 ± 18.32	24 – 116	0.226
MABP (mmHg)	95.50 ± 15.30	62 – 141	95.80 ± 15.07	60 – 154	0.971
HR (beats/min)	79.42 ± 16.61	26 – 152	76.76 ± 14.03	40 – 120	0.086

Data are shown as mean ± standard deviation and minimum to maximum values. HTN: hypertension; EX: exercise training; F: female; M: male; BMI: body mass index; Rf: respiratory frequency; SpO2: arterial oxygen saturation; SBP: systolic blood pressure; DBP: diastolic BP; PP: pulse pressure; MABP: mean arterial BP; HR: heart rate. Data were analyzed using Mann-Whitney non-parametric test. A $p<0.05$ was considered significant.

Table 4. Multiple logistic regression.

Variable	Odds ratio	Standard error	95% CI	|Z|	p-value
EX	0.448	0.153	0.230 to 0.873	-2.360	**0.018**
Sex (male)	3.121	1.087	1.576 to 6.178	3.270	**0.001**
Steroids	0.949	0.325	0.485 to 1.858	-0.150	0.881
Antibiotic	1.457	0.509	0.733 to 2.893	1.080	0.282
Anticoagulant	1.152	0.424	0.559 to 2.371	0.380	0.701
Insulin	0.488	0.305	0.143 to 1.664	-1.150	0.252
IMV	2.287	0.965	0.999 to 5.233	1.960	0.050
NIMV	5.964	1.997	3.093 to 11.497	5.330	**<0.001**
ECMO	0.055	0.022	0.024 to 0.125	-6.990	**<0.001**

EX: exercise training; IMV: invasive mechanical ventilation; NIMV: non-invasive mechanical ventilation; ECMO: extracorporeal membrane oxygenation. The significance was set to $p<0.05$.



Control
EX
1.0
0.5
0.0
Probability of Survival
n=201
*p=0.027
n=238
0
20
40
60
80
Time (days)