Brazilian Cardiology Interventional Registry during COVID-19 pandemic (RBCI-COVID19)

Registro Brasileiro da Cardiologia Intervencionista durante a pandemia da COVID-19 (RBCI-COVID19)

Viviana Guzzo Lemke^{1ID}, Maria Sanali Moura Paiva^{2ID}, Giordana Zeferino Mariano^{3ID}, Marcelo Antônio Cartaxo Queiroga Lopes^{4ID}, Ricardo Alves da Costa⁵, Gláucia Maria Moraes de Oliveira^{6ID}

DOI: 10.31160/JOTCI202028A202010

¹ Hospital das Nações, Curitiba, PR, Brazil.

² Universidade Federal do Rio Grande do Norte, Natal, RN, Brazil.

³ Hospital São João Batista, Criciúma, SC, Brazil.

⁴ Sociedade Brasileira de Cardiologia, Rio de Janeiro, RJ, Brazil.

⁵ Instituto Dante Pazzanese de Cardiologia, São Paulo, SP, Brazil.

⁶ Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil.

ABSTRACT – Background: The outbreak of coronavirus disease 2019 (COVID-19), a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was characterized as a pandemic by the World Health Organization, with high fatality rate. The number of registered cases has skyrocketed, as well as the number of deaths. Half of the patients with COVID-19 have chronic conditions, especially cardiovascular and cerebrovascular diseases, followed by diabetes mellitus, increasing their morbidity and mortality. Several studies have demonstrated this correlation, however a concomitant SARS-CoV-2 infection may trigger new clinical manifestations, such as myocarditis, arrhythmias, left ventricular dysfunction, systemic embolism and myocardial infarction, and this need to be understood within the context of each country's reality. Delays in diagnosis and treatment of these patients could result in a poorer prognosis. **Methods:** This will be a prospective, multicenter registry including approximately 2,000 patients in 40 cath labs in Brazil. We will include male and female patients, aged over 18 years, admitted to interventional cardiology labs to perform a cardiovascular procedure during the COVID-19 pandemic. The primary outcomes will be death from any cause, acute myocardial infarction and stroke, and need for reintervention. As secondary outcomes, we will observe delays in completing the procedures due to the COVID-19 pandemic, and symptom-to-door, door-to-balloon, and door-to-table times. The availability and proper use of standard personal protective equipment will also be analyzed. **Conclusion:** The analysis of the outcomes of this multicenter registry will allow for a better understanding of the scenario of cardiovascular diseases during the COVID-19 pandemic in interventional clinical practice in Brazil.

Keywords: Coronavirus infections; COVID-19; Pandemics; Interventional cardiology; Medical registries; Brazil

How to cite this article:

Lemke VG, Paiva MS, Mariano GZ, Lopes MA, Costa RA, Oliveira GM. Brazilian Cardiology Interventional Registry during COVID-19 pandemic (RBCI-COVID19). J Transcat Intervent 2020;28:eA202010. <https://doi.org/10.31160/JOTCI202028A202010>

Corresponding author:

Viviana Guzzo Lemke
Rua Raphael Papa, 10 – Jardim Social
Zip code: 82530-190 – Curitiba, PR, Brazil
E-mail: vivianalemke@terra.com.br

Received on:

May 22, 2020

Accepted on:

Jun 10, 2020

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RESUMO – Introdução: O surto da doença pelo coronavírus 2019 (COVID-19), provocada pelo coronavírus da síndrome respiratória aguda grave 2 (SARS-CoV-2), foi caracterizado como pandemia pela Organização Mundial da Saúde e apresenta alta letalidade. O número de casos registrados tem aumentado vertiginosamente, assim como o número de óbitos. Metade dos pacientes com COVID-19 tem condições crônicas, em especial doenças cardiovasculares e cerebrovasculares, seguidas por diabetes melito, elevando sua morbimortalidade. Diversos estudos têm demonstrado essa correlação, contudo muitas novas manifestações clínicas, como miocardite, arritmias, disfunção ventricular esquerda, embolia sistêmica e infarto do miocárdio podem ser precipitadas pela concomitância da infecção pelo SARS-CoV-2 e precisam ser entendidas dentro na realidade de cada país. O atraso no atendimento destes pacientes parece acrescentar pior prognóstico. **Métodos:** Este registro prospectivo, multicêntrico, incluirá aproximadamente 2.000 pacientes em 40 centros de hemodinâmica no Brasil. Serão incluídos pacientes de ambos os sexos, com idade superior a 18 anos, admitidos nos laboratórios de cardiologia intervencionista para realização de procedimento cardiovascular, enquanto durar a pandemia pela COVID-19. Os desfechos primários serão ocorrência de morte por qualquer causa, infarto agudo do miocárdio e acidente vascular cerebral e necessidade de reintervenções. Como desfechos secundários, serão observados retardo na realização dos procedimentos decorrentes da pandemia pela COVID-19 e tempos sintomas-porta, porta-balão e porta-mesa. Também serão analisados a disponibilidade e o uso adequado dos Equipamentos de Proteção Individual padronizados. **Conclusão:** A análise dos resultados deste registro multicêntrico permitirá conhecer o cenário das

doenças cardiovasculares relacionadas ao período da pandemia de COVID-19 na prática clínica intervencionista brasileira.

Descritores: Infecções por coronavírus; COVID-19; Pandemias; Cardiologia intervencionista; Registros médicos; Brasil

INTRODUCTION

On March 11, 2020, the World Health Organization (WHO) characterized the outbreak of the coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as a pandemic.¹ After 66 days of this announcement, the confirmed cases reported have achieved more than 5 million in 188 countries, with approximately 332,000 deaths, most in the United States, United Kingdom, Italy, France, Spain and Brazil. To date, May 21st, 2020, Brazil has recorded approximately 310 thousand cases and 20 thousand deaths, with an estimated lethality rate of 6.46%. These numbers have been increasing rampantly since the beginning of the pandemic.²

Half of the patients with COVID-19 have chronic conditions, especially cardiovascular (CVD) and cerebrovascular diseases, followed by diabetes mellitus, increasing their morbidity and mortality.³ A meta-analysis of six studies conducted in China, including 1,527 patients with COVID-19, evaluated the prevalence of CVD and showed the following: 17.1% with hypertension, 16.4% with cardiac and cerebrovascular disease, and 9.7% with diabetes mellitus.⁴ Another study with 44,672 confirmed cases of COVID-19 in China reported the presence of pre-existing comorbidities, such as CVD (10.5%), diabetes mellitus (7.3%), and hypertension (6%), which were associated with a lethality rate of 2.3%.⁵ These findings point to the importance of CVD in the context of COVID-19. However, these studies were not adjusted for sex and age, and many did not provide complete data, and may have been prone to bias in selection and measurements.

The latter aspect becomes more significant when taking into account that males are more susceptible to COVID-19, and there is a higher mortality rate in elderly patients. Murine models and human autopsy samples have shown that SARS-CoV-2 can down-regulate myocardial and pulmonary angiotensin-converting enzyme 2 (ACE2) pathways, thereby mediating myocardial inflammation, pulmonary edema and acute respiratory failure, which might explain the cardiovascular involvement in critically ill patients.⁶ Experimental data have shown that 17 β -estradiol increases the expression and activity of ACE2 in both adipose tissue and kidney, and hypertensive male mice have higher expression of myocardial ACE2 than females, and its levels decreased after orchiectomy. On the other hand, minimally invasive necropsy studies reported the presence of SARS-CoV-2 in the testicles. This is one of the hypotheses for the difference in lethality rates between sexes observed in the studies.⁷⁻⁹

Myocardial injury occurs in 8% to 12% of cases of COVID-19. Direct myocardial injury, systemic inflammation effects, myocardial oxygen demand-supply mismatch, acute coronary event, a state of hypercoagulability and endothelial dysfunction appear to be the most common mechanisms responsible for cardiac injury and have been associated with increased levels of biomarkers, such as troponin I, B-type natriuretic peptide (BNP), and D-dimer.¹⁰⁻¹⁵ When treating patients with COVID-19, cardiologists should be aware of new clinical manifestations, such as myocarditis, arrhythmias, left ventricular dysfunction and systemic embolism, which may be associated with the condition, as well as the occurrence of a myocardial infarction triggered by the concomitant SARS-CoV-2 infection.¹⁶⁻¹⁹

The COVID-19 pandemic could also affect delivery of care to patients with acute CVD, such as acute myocardial infarction (MI). The definition of acute MI management in patients with COVID-19 must take into account the resources locally available, such as: effective cath labs, coronary care unit and/or intensive care unit (ICU) beds, and adequate safety and protection measures against COVID-19.^{19,20} The *Sociedade Brasileira de Hemodinâmica e Cardiologia Intervencionista* (SBHCI) recommends postponing the performance of elective procedures in infected or suspected patients; limit the performance of cath lab procedures to situations of cardiovascular emergency (in cases with no instability criteria, postpone them until a non-infective phase); in services with more than one cath lab, it is recommended that one of them is reserved for procedures in infected patients.²¹

In cases of ST-segment elevation myocardial infarction (STEMI) with hemodynamic stability, fibrinolysis may be an alternative in COVID-19 positive patients during respiratory epidemics, which renders it necessary to categorize these patients in risk levels. Length of hospital stay while waiting for additional procedures for complete revascularization is an important concern. Decisions must be individualized, considering the risk of exposure to COVID-19 versus the risk of delay in diagnosis or therapy.²⁰⁻²² In addition, it is important to distinguish MI caused by unstable plaque rupture from type 2 MI or myocarditis on the differential diagnosis of AMI.¹⁰⁻¹⁵

The challenges imposed during the pandemic are great, not only in the management of patients with CVD who need to continue their treatment and may or may not be affected by COVID-19, but also in the treatment of the complex cardiovascular manifestations of SARS-CoV-2, such as myocarditis, Takotsubo cardiomyopathy, and myocardial injury, which can mimic STEMI. Adding to this equation are a delayed care seeking due to fear of contamination, an increased incidence of MI with and without obstructive lesion, and a poorer prognosis in cases of myocardial infarction associated with COVID-19.²⁰⁻²⁵

A study reporting the experience of Campania, Italy, during 60 days, starting in January 2020, showed that there

was a reduction in the incidence of percutaneous coronary interventions (PCI) for MI, from 178 to 120 PCI/100 thousand inhabitants, during a 4-week period before and after the COVID-19 outbreak (incidence rate=0.68), with a reduction in both ST-segment elevation MI and non-ST-segment elevation MI (from 80 to 54, and from 98 to 66 PCI/100 thousand inhabitants per year, respectively). The decrease was more evident in female and elderly patients.²⁶ Data from Chinese patients during COVID-19 demonstrated numerically greater median times in all components when compared to historical data from the previous year (time from onset of symptoms to the first medical contact, door-to-device time, cath lab arrival time). The greatest difference found was in the interval between the onset of symptoms and the first medical contact.²⁷

New prospective studies need to be conducted to assess the care delivered to patients with heart disease during the COVID-19 pandemic. The objective of the Brazilian Interventional Cardiology Registry during the COVID-19 pandemic (RBCI-COVID19) will be to report the care of patients with heart disease during the COVID-19 pandemic who will need assistance in the Interventional Cardiology laboratories of the participant hospitals, during a 4-month period, or while the COVID-19 pandemic lasts (Figure 1). We also intend to record clinical, laboratory, and imaging variables, the outcomes upon admission and the outcomes resulting from procedures performed in interventional cardiology laboratories. We will also observe whether the differences reported between sexes and age groups will be replicated in the cases reported in Brazil.

Figure 1. Logo of the Brazilian Interventional Cardiology Registry during the COVID-19 pandemic.

METHODS

Selection of patients and inclusion and exclusion criteria

This is a prospective, multicenter registry, including approximately 2,000 patients in 40 cath labs in Brazil. Male and female patients, aged over 18 years, admitted to interventional cardiology laboratories for cardiovascular procedures will be included. Patients who refuse to sign the Informed Consent Form or those whose legal guardians refuse consent (<https://www.mulheresemacao.online/rbci-covid19>) will be excluded from the study, as well as peripheral, neurological and vascular intervention

procedures and placement of devices for artificial cardiac stimulation.

Participating centers

The participating centers were included by spontaneous registration and by invitation sent through social media, telephone and WhatsApp to cath labs in all regions of Brazil. The included centers and their managers are listed in table 1.

Table 1. Study participating centers and principal investigator

Principal investigator	Organization
Alysson Moço Faidiga/Marcos Hertz	Clínica Angiopar, São José dos Pinhais (PR)
Ana Tereza Azeredo Bastos	Hospital das Clínicas da Universidade Federal de Goiás, Goiânia (GO)
André Francisco de Paula Antonangelo	Hospital Universitário Onofre Lopes, Natal (RN)
Antonio Augusto Farias	Hospital Prontocor, Rio de Janeiro (RJ)
Cesar de Oliveira Lopes Dusilek	Hospital do Rocio, Campo Largo (PR)
Cristiano Guedes/Thais C. V. Tamazato	Hospital Ana Nery, Salvador (BA)
Cyro Rodrigues	Hospital de Caridade São Vicente de Paulo, Jundiá (SP)
Danilo Maksud	Hospital das Clínicas Luiza de Pinho Melo, Mogi das Cruzes (SP)
Eder Voltolini	Hospital Nossa Senhora Aparecida, Umuarama (PR)
Edgard Quintella	Instituto Estadual de Cardiologia Aloysio de Castro/Instituto do Coração de Petrópolis, Rio de Janeiro/Petrópolis (RJ)
Ênio Eduardo Guérios	Hospital Pilar/Hospital de Clínicas da Universidade Federal do Paraná, Curitiba (PR)
Esmeraldi Ferreira	Hospital Universitário Pedro Ernesto, Rio de Janeiro (RJ)
Felipe Bortot César	Hospital Santa Rita de Cássia, Vitória (ES)
Fernanda Marinho Mangione/José Armando Mangione	A Beneficência Portuguesa de São Paulo, São Paulo (SP)
Flávio Azevedo/Rodrigo Cantarelli	Hospital Metropolitano Sul Don Hélder Câmara, Cabo de Santo Agostinho (PE)
Frederico Toledo Campo Dall'Orto	Hospital do Coração de Poços de Caldas, Poços de Caldas (MG)
Gabriella de Araújo Cunha Lima Nóbrega	Hospital Alberto Urquiza Wanderley, João Pessoa (PB)
Giordana Zeferino Mariano	Hospital São João Batista, Criciúma (SC)
Gustavo Ithamar Souto Maior	Instituto Neuro Cardiovascular de Campina Grande, Campina Grande (PB)
Luciano de Moura Santos	Hospital Santa Lúcia, Brasília (DF)
Luís Fernando Alves Campos	Hospital do Coração, Natal (RN)
Luiz Kohn	Hospital Universitário Severino Sombra, Vassouras (RJ)
Marcel Rogers Ravanelli	Hospital Universitário Evangélico Mackenzie, Curitiba (PR)
Marcelo Harada	SOS Córdio, Florianópolis (SC)
Marcio José da Costa Montenegro	Hospital Casa São Bernardo, Rio de Janeiro (RJ)
Maria Cristina Meira Ferreira	Hospital Federal dos Servidores do Estado, Rio de Janeiro (RJ)
Mayara Viana	Hospital São Rafael, Imperatriz (MA)
Rafael de Souza Henud	Hospital CEMERU, Rio de Janeiro (RJ)
Renato Serpa	Hospital Santa Casa de Misericórdia de Vitória, Vitória (ES)
Ricardo Barbosa	Fundação Santa Casa de Misericórdia de Franca, Franca (SP)
Ricardo Monteiro Lourenço	Hospital Angelina Caron/Hospital Pilar, Campina Grande do Sul/Curitiba (PR)
Rodrigo Costa Guerreiro	EMCOR (Hospital do Coração de Nova Iguaçu), Rio de Janeiro (RJ)
Stefan Costa Silveira	Hospital das Nações, Curitiba (RJ)
Wangles Jotão Geraldo	Hospital Promater, Natal (RN)
Wellingson Guimarães	Hospital Antônio Prudente, Natal (RN)

Operational procedures and outcomes

The procedures to be analyzed during the study are shown in figure 2. The primary outcomes will be the occurrence of death from any cause, MI and stroke, and the need for reinterventions. As secondary outcomes, we will observe delays in completing the procedures due to the COVID-19 pandemic, and symptom-to-door, door-to-balloon, and door-to-table times, as shown in figure 3. The availability and proper use of standard personal protective equipment (PPE) will also be analyzed.²⁸

ICF: Informed Consent Form; MI: myocardial infarction.

Figure 2. Procedures to be performed in the cath lab and 30 days after the intervention.

MI: acute myocardial infarction.

Figure 3. Definition of times related to delays in performing cath lab procedures due to the COVID-19 pandemic. “Symptom-to-door” time is the time interval between the onset of the main symptom reported by the patient and the arrival at the hospital. “Door-to-balloon” time is the time interval between the patient’s arrival at the hospital and the time of a catheter guidewire crossing the culprit lesion caused by acute myocardial infarction. “Door-to-table” time is the time interval between the patient’s arrival at the hospital and the start of the diagnostic procedure in the cath lab.

Data collection

Information about the study will be presented to potential research participants (or their legally authorized representative) and/or impartial witness, and questions will be asked to determine possible eligibility. The screening procedures will start only after the Informed Consent Form is presented, discussed and signed. The study will have a telephone number for direct contact with one of the study coordinators, as well as messages via WhatsApp, which will be answered immediately, about patients’ eligibility and data collection, as well as their insertion in the database.

The data will be collected from standardized electronic files, via the internet, on e-CRF (<https://covid.rbcj.online>), and will be inserted by the center’s teams, who will be duly trained by the coordinating center. All patients included in the study will have their clinical data and information that are relevant to the study collected by qualified personnel trained in confidentiality of information and safe storage procedures. Clinical data collected from volunteers who eventually decide to terminate their participation during the study will be collected and stored from the date of their inclusion until their participation termination date. Confidentiality of data and access to electronic platforms will be protected by the investigators at hospitals sites, who will maintain privacy and confidentiality of information, according to the requirements set by national regulatory agencies. The e-CRF must be filled in immediately after the inclusion of the patient, based on source documents. All staff members must be formally authorized by the principal investigator of the research center and properly trained in their role within the study. In the electronic data processing performed by the proposer of the study, after reviewing the e-CRFs, additional information requests may be generated, due to discrepancies. These data must be confirmed or modified by the investigator within 3 working days.

Statistical analysis

For data analysis, the Software R²⁹ (R CORE TEAM, 2019) will be used. The tests initially employed will be the Kolmogorov-Smirnov test, the Mann-Whitney test, the Kruskal-Wallis test and the Chi-squared test. The results will be presented as frequency, mean $\pm$ standard deviation, median and interquartile range, and they will be considered significant when $p < 0.05$.

Parametric models will also be prepared, with regressions estimated with elastic net for the choice of relevant covariates, and then re-estimated with significant and non-parametric variables, with classification and regression trees (CART), with the resulting variables of parametric models.³⁰

Ethical aspects

The study will be carried out in accordance with the Brazilian and international standards described in the Brazilian resolution 466/12 and in the documents of the Ministry of Health Guidelines for Good Clinical Practice, Amendment 6 –

Revision 2 (<http://portal.anvisa.gov.br/>). The study protocol, the Informed Consent Form and other documents pertinent to this research were allocated by the Research Ethics Committee of the coordinating center, sent for evaluation by the National Research Ethics Commission (CONEP, acronym in Portuguese), and approved in protocol CAAE 30564720.0.0000.5292. All patients selected to participate in the study will sign the Informed Consent Form before any registration pertinent to the study is made. For those with severe health conditions, assent will be given by legal representatives. Survey participants or their legal representatives will be informed that their participation is voluntary and that they may withdraw their consent to participate at any time. They will be informed that, since this is a real-world observational study, the decision to participate or not in the registration will not affect the care they will receive to treat their condition.

Confidentiality

No patient identification data will be released. The data capture system will identify patients and centers by numbers. Data from printed medical records will be kept confidential by each participating center, stored in locked cabinets/drawers. The patients' confidentiality will be preserved in all reports and in all phases of the study.

Temporality of data collection

The registry began collecting data in May 2020 and will last for 120 days, or as long as the COVID-19 pandemic lasts.

Data quality management

Various procedures will guarantee the quality of the data, including the following: all researchers will participate in a training session before the study starts, to ensure consistency of data collection; a telephone line will be available 7 days a week, 24 hours a day, for the participating centers to submit their questions and have them answered by the coordinating center; all data entered into the Data Management System will undergo several verification checks by the coordinating center; the investigator who inserts the data is notified at the time of insertion of any inconsistency; statistical techniques for identifying inconsistency and fraud will be conducted periodically (approximately every 15 days); monitoring at the centers will be carried out during the study in a remote online format; the coordinating center will review detailed reports on screening, inclusion, follow-up, consistency and data completeness on a monthly basis.

Guidelines for publication

The results will be published with the Study Steering Committee as authors, on behalf of the researchers, who will be cited at the end of the article. Up to three members (at the discretion of the principal investigator) will be considered per research team that participated in each phase

of the study. Requests for inclusion of other names will be evaluated individually by the Publication Committee. The investigator may, after the first publication of the study, request the availability of data for use in publications, upon prior presentation of a research project protocol approved by the CEP and by the registry's executive and steering committee.

Study budget

The procedures performed during the research will not be reimbursed, since this is an observational study to verify the impact of the COVID-19 pandemic on patients with heart disease who were treated in Brazilian cathlabs.

Declaration of conflicts of interest

The study coordinators have no conflicts of interest to disclose in this study.

Organization

Study Steering Committee: Viviana Guzzo Lemke, Maria Sanali Moura Paiva, Giordana Zeferino Mariano, Gláucia Maria Moraes de Oliveira and Ricardo Alves da Costa.

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