Impact of Diabetes in Patients Waiting for Invasive Cardiac Procedures During COVID-19 Pandemic

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Abstract

**Background:** During COVID-19 pandemic, elective invasive cardiac procedures (ICP) have been frequently cancelled or postponed. Consequences may be more evident in patients with diabetes.

**Objectives:** The objective was to identify the peculiarities of patients with DM among those in whom ICP were cancelled or postponed due to the COVID-19 pandemic, as well as to identify subgroups in which the influence of DM has higher impact on the clinical outcome.

**Methods:** We included 2,158 patients in whom an elective ICP was cancelled or postponed during COVID-19 pandemic in 37 hospitals in Spain. Among them, 700 (32.4%) were diabetics. Patients with and without diabetes were compared.

**Results:** Patients with diabetes were older and had a higher prevalence of other cardiovascular risk factors, previous cardiovascular history and co-morbidities. Diabetics had a higher mortality (3.0% vs. 1.0%; \( p=0.001 \)) and cardiovascular mortality (1.9% vs. 0.4%; \( p=0.001 \)). Differences were especially important in patients with valvular heart disease (mortality 6.9% vs 1.7% [\( p<0.001 \)] and cardiovascular mortality 4.9% vs 0.9% [\( p=0.002 \)] in patients with and without diabetes, respectively). In the multivariable analysis, diabetes remained as an independent risk factor both for overall and cardiovascular mortality. No significant interaction was found with other clinical variables.

**Conclusion:** Among patients in whom an elective invasive cardiac procedure is cancelled or postponed during COVID-19 pandemic, mortality and cardiovascular mortality is higher in patients with diabetes, irrespective on other clinical conditions. These procedures should not be cancelled in patients with diabetes.

Introduction

The ongoing COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared by the World Health Organization (WHO) in March 2020\(^1\). By January 2021, almost 100 million people had suffered the disease, and nearly 2 million have died worldwide. Apart from these direct consequences, health care systems have been severely overwhelmed, negatively impacting on the management of other patients that usually require prompt treatment, especially those with cardiovascular diseases\(^2\text{-}\text{8}\). Specifically, patients pending on invasive cardiac procedures (ICP) have been cancelled or postponed in many centers, and this may have fatal consequences for some patients, as we have recently shown in a multicenter study from Spain\(^9\).

Cardiovascular diseases constitute the main cause of death in patients with diabetes mellitus (DM)\(^10\), and among patients with cardiovascular diseases, those with DM are at an especially high risk of death\(^11\text{-}12\). Because of that, waiting list in patients pending on cardiovascular procedures that have been postponed due to the pandemic may have especial impact among diabetics\(^9\).
The objective was to identify the peculiarities of patients with DM among those in whom ICP were cancelled or postponed due to the COVID-19 pandemic, as well as to identify subgroups in which the influence of DM has higher impact on the clinical outcome.

**Methods**

**Study population.**

We have previously published the outcome of patients in whom elective ICP were cancelled or postponed when the state of alarm due to the COVID-19 pandemic was declared in Spain on the 14th of March 2020. In this study, 2,158 patients were included in 37 hospitals.

At the time of the publication of that study, DM status was known in 2,110, whereas no information was available for 48 patients. For this sub-study, additional efforts, directly contacting with the patient or obtaining documents from the referral centers, we could obtain DM status for all 2,158 patients.

**Data collection and follow-up.**

Data were entered in an electronic database (pInvestiga, Moaña, Pontevedra, Spain). Clinical variables, such as main cardiovascular disease pending on treatment, type of procedure pending to be performed, clinical situation, and cardiovascular risk factors, were collected.

Patients were followed-up until the 30th of April 2020 (45 days). Patients with DM were compared with those without DM, regarding type of pending procedure, main cardiovascular disease, functional class for heart failure and angina, and other clinical variables. The influence of DM in different patient subgroups was evaluated.

**Definitions.**

Coronary angiography and/or PCI as the type of pending procedure included coronary angiography in patients with previously diagnosed or suspected CAD, and those with previously known CAD pending on PCI (e.g. stage procedures). Coronary angiography to rule out CAD as the underlying cause of left ventricular dysfunction was also included in this category. However, coronary angiography as part of the study of patients pending on any type of surgical intervention was included in a different category, because the main underlying condition was considered to be the disorder pending to be treated (e.g. valvular heart disease) rather than the eventual bystander of coronary artery disease. Other procedures included transcatheter aortic valve implantation (TAVI), percutaneous mitral valve repair, left atrial appendage closure, percutaneous closure of ASD, or treatment of tricuspid regurgitation.

**Statistical analysis.**

Continuous variables are presented as mean ± standard deviation and compared using the Student t-test or appropriate non-parametric tests. Discrete variables are presented as percentages (proportions), and
compared with the Chi-square test, using Fisher correction when needed. Statistical analysis was done using the SPSS statistical package (Chicago, Illinois). Associations were considered statistically significant when \( p < 0.05 \), although all \( p \) values are presented. Univariable and multivariable analysis were conducted in order to identify independent risk factors for mortality, and for secondary endpoints.

**Results**

**Type of pending procedure.**

Out of the 2,158 patients, 700 (32.4%) were DM. Figure 1 shows the type of pending procedure in patients with and without DM. Coronary diagnostic and/or therapeutic intervention was the most frequent pending procedure both groups of patients, but it was more frequent in DM than in non-DM (61.5% vs. 49.5%, respectively; \( p < 0.001 \)). The second type of procedure was percutaneous valvular intervention, that accounted for 17.9% and 16.2% for DM and non-DM, respectively (\( p = 0.300 \)). Other diagnostic procedure was pending in 14.2% and 25.2% of DM and non-DM patients, respectively (\( p < 0.001 \)). Other therapeutic procedure was pending in 6.7% and 9.1% in patients with and without DM, respectively (\( p = 0.060 \)).

**Comparison of patients with and without DM.**

Table 1 shows the differences among patients with and without DM related with clinical characteristics. Patients with DM were older, and had a higher prevalence of hypertension, hypercholesterolemia, chronic renal failure, peripheral artery disease, and previously diagnosed coronary artery disease including previous infarction, and previous myocardial revascularization both percutaneous and surgical. Left ventricular dysfunction was more frequently present in patients with DM. Functional class for heart failure (NYHA) was similar for patients with and without DM, but functional class for angina (CCS) was worse for patients with DM.
|                  | Yes (n = 691) | No (1,419) | P value |
|------------------|--------------|------------|---------|
| Age              | 72.3 ± 10.0  | 69.2 ± 12.7| < 0.001 |
| Age ≥ 80 (%)     | 24.9         | 21.4       | 0.078   |
| Female gender (%)| 34.9         | 39.9       | 0.066   |
| Hypertension (%) | 82.9         | 59.8       | < 0.001 |
| Hypercholesterolemia (%) | 71.0 | 47.9 | < 0.001 |
| Smoking (%)      | 30.8         | 29.3       | 0.483   |
| Chronic renal failure (%) | 13.2 | 7.5 | < 0.001 |
| Peripheral artery disease (%) | 14.2 | 9.0 | < 0.001 |
| Previous CAD (%) | 41.7         | 27.4       | < 0.001 |
| Previous infarction (%) | 17.9 | 11.4 | < 0.001 |
| Previous PCI (%) | 23.6         | 15.5       | < 0.001 |
| Previous CABG (%)| 6.7          | 3.4        | 0.001   |
| Previous valve replacement (%) | 3.5  | 4.9  | 0.144   |
| Left ventricular dysfunction (%) | 27.1 | 21.4 | 0.033   |
| NYHA > II (%)    | 20.1         | 19.0       | 0.282   |
| CCS > II (%)     | 10.0         | 8.4        | 0.001   |
| Main cardiovascular condition (%) |         | < 0.001   |
| Ischemic heart disease | 57.6 | 47.0 |
| Valvular heart disease   | 29.2 | 36.9 |
| Other             | 13.3         | 16.2       |         |

Among the 2,158 patients, 559 had previously documented coronary artery disease. Patients with DM had higher frequency of multi-vessel disease (72.9% vs. 56.7% in non-DM, p < 0.001). Left main disease was
also more frequent in patients with DM, but differences were not statistically significant (13.9% vs. 9.8% in non-DM, p = 0.133).

**Influence of DM on clinical outcomes.**

During the 45-day follow-up period, 36 patients died (1.7%), most of them due to cardiovascular causes (n = 19, 59.4%). Patients with DM had a higher rate of both overall mortality (3.0% vs. 1.0% in non-DM, p = 0.001) and cardiovascular mortality (1.9% vs. 0.4% in non-DM, p = 0.001), whereas differences in non-cardiovascular mortality were not statistically different (1.1% vs 0.6% in DM and non-DM, respectively; p = 0.196).

In the multivariable analysis, DM remained as an independent risk factor both for overall and cardiovascular mortality (Fig. 2).

The proportion of patients that underwent an urgent procedure due to clinical instabilization was also significantly higher in patients with DM (10.4% vs. 7.3% in non-DM; p = 0.015).

During the study period, 12 patients with DM (2.3%) and 21 without DM (1.4%) had a diagnosis of COVID-19 by protein-chain reaction test for SARS-CoV-2 (p = 0.157).

**Mortality in patients with and without DM among different subgroups.**

Mortality and cardiovascular mortality were higher in patients with DM regardless the main cardiovascular disease, although differences were statistically significant only for those patients with valvular heart disease (Figs. 3.A and 3.B).

Figure 4 shows the mortality and cardiovascular mortality in patients with and without DM in the most frequent types of pending procedures. Mortality and cardiovascular mortality were higher in patients pending on coronary diagnostic or therapeutic procedures, TAVI, and other diagnostic procedures, but differences reached statistical significance only for cardiovascular mortality in patients pending on TAVI. In patients pending on LAAC, mortality was higher in non-DM but differences were not statistically different.

Tables 2 and 3 show the overall and cardiovascular mortality in patients with and without DM in different patient subgroups accordingly to clinical characteristics. No significant interaction was found between DM and other clinical variables (Table 4).
Table 2
Mortality in patients with and without DM in different patients subgroups. PCI: Percutaneous coronary intervention. CABG: Coronary artery bypass grafting. NYHA: New York Heart Association. CCS: Cardiology Canadian Society.

| Factor present                              | Yes | Non-DM | P value | Yes | Non-DM | P value |
|---------------------------------------------|-----|--------|---------|-----|--------|---------|
| Age > 80 (%)                                | 7.5 | 3.8    | 0.071   | 1.5 | 0.3    | 0.006   |
| Female gender (%)                           | 5.0 | 1.2    | 0.001   | 2.0 | 0.9    | 0.098   |
| Hypertension (%)                            | 3.3 | 1.1    | 0.003   | 0.0 | 0.7    | 0.362   |
| Hypercholesterolemia (%)                    | 3.3 | 1.2    | 0.012   | 1.5 | 0.7    | 0.378   |
| Smoking (%)                                 | 1.0 | 0.2    | 0.262   | 3.4 | 1.2    | 0.004   |
| Chronic renal failure (%)                   | 9.9 | 2.8    | 0.036   | 2.0 | 0.9    | 0.044   |
| Peripheral artery disease (%)               | 3.1 | 3.1    | 1.000   | 3.0 | 0.8    | < 0.001 |
| Previous CAD (%)                            | 2.4 | 1.8    | 0.537   | 3.0 | 0.7    | 0.001   |
| Previous infarction (%)                     | 2.4 | 0.6    | 0.314   | 3.1 | 1.1    | 0.002   |
| Previous PCI (%)                            | 2.4 | 0.4    | 0.165   | 3.2 | 1.1    | 0.003   |
| Previous CAGB (%)                           | 0.0 | 6.3    | 0.242   | 3.2 | 0.9    | < 0.001 |
| Previous valve replacement (%)              | 4.3 | 1.5    | 0.444   | 2.6 | 0.8    | 0.002   |
| Left ventricular dysfunction (%)            | 1.6 | 0.7    | 0.370   | 3.2 | 1.0    | 0.001   |
| NYHA > 2 (%)                                | 7.1 | 2.5    | 0.061   | 2.1 | 0.7    | 0.014   |
| CCS > 2 (%)                                 | 4.8 | 3.9    | 1.000   | 2.7 | 0.7    | 0.001   |
Table 3
Cardiovascular mortality in patients with and without DM in different patients subgroups. PCI: Percutaneous coronary intervention. CABG: Coronary artery bypass grafting. NYHA: New York Heart Association. CCS: Cardiology Canadian Society.

| Factor present             | Yes | Non-DM | P value | Yes | Non-DM | P value |
|----------------------------|-----|--------|---------|-----|--------|---------|
| Age > 80 (%)               | 4.6 | 1.9    | 0.093   | 1.0 | 0.0    | 0.003   |
| Female gender (%)          | 4.1 | 0.5    | 0.001   | 0.7 | 0.3    | 0.409   |
| Hypertension (%)           | 2.3 | 0.5    | 0.002   | 0.0 | 0.2    | 1.000   |
| Hypercholesterolemia (%)   | 2.0 | 0.6    | 0.023   | 1.5 | 0.1    | 0.032   |
| Smoking (%)                | 0.5 | 0.0    | 0.335   | 2.3 | 0.5    | 0.002   |
| Chronic renal failure (%)  | 7.7 | 1.9    | 0.083   | 1.0 | 0.3    | 0.079   |
| Peripheral artery disease (%) | 0.0 | 0.0    | 1.000   | 2.2 | 0.5    | < 0.001 |
| Previous CAD (%)           | 1.4 | 0.5    | 0.244   | 2.3 | 0.4    | 0.002   |
| Previous infarction (%)    | 0.8 | 0.6    | 1.000   | 2.1 | 0.4    | < 0.001 |
| Previous PCI (%)           | 1.8 | 0.4    | 0.312   | 1.9 | 0.4    | 0.004   |
| Previous CAGB (%)          | 0.0 | 2.1    | 1.000   | 2.0 | 0.4    | < 0.001 |
| Previous valve replacement (%) | 4.3 | 0.0    | 0.253   | 1.7 | 0.4    | 0.002   |
| Left ventricular dysfunction (%) | 1.1 | 0.7    | 0.635   | 2.2 | 0.4    | 0.001   |
| NYHA > 2 (%)               | 5.1 | 1.2    | 0.049   | 1.6 | 0.2    | 0.004   |
| CCS > 2 (%)                | 3.2 | 2.9    | 1.000   | 1.8 | 0.2    | < 0.001 |
Table 4
Interaction between different variables and the effect of diabetes on mortality and cardiovascular mortality.

| P for interaction | Mortality | Cardiovascular mortality |
|-------------------|-----------|--------------------------|
| Age > 80 (%)      | 0.192     | 0.990                    |
| Female gender (%) | 0.353     | 0.0176                   |
| Hypertension (%)  | 0.996     | 0.996                    |
| Hypercholesterolemia (%) | 0.774 | 0.375 |
| Smoking (%)       | 0.799     | 0.994                    |
| Chronic renal failure (%) | 0.499 | 0.790 |
| Peripheral artery disease (%) | 0.128 | 1.000 |
| Previous CAD (%)  | 0.102     | 0.478                    |
| Previous infarction (%) | 0.774 | 0.361 |
| Previous PCI (%)  | 0.550     | 0.950                    |
| Previous CABG (%) |           |                          |
| Previous valve replacement (%) | 0.976 | 0.997 |
| Left ventricular dysfunction (%) |           |                          |
| NYHA > 2 (%)      | 0.953     | 0.561                    |
| CCS > 2 (%)       | 0.212     | 0.066                    |

Discussion

Among patients in whom an elective cardiac invasive procedure was cancelled or postponed, those with DM had a significantly higher mortality, mainly due to a higher cardiovascular mortality. Overall mortality was 3 times higher and cardiovascular mortality 4.75 times higher in DM in comparison with patients without DM.

Patients with DM had a worse clinical profile, including more advanced age, and higher prevalence of additional cardiovascular risk factors, previous cardiovascular diseases, and some co-morbidities, such as renal failure. However, DM was an independent predictor both for mortality and cardiovascular mortality, indicating that DM per se is a risk factor in this special population. The main practical implication of these findings is that elective invasive cardiac procedures should be prioritized in patients with DM. That is, during COVID-19 pandemic, invasive cardiac procedures should not be postponed in
patients with DM. Event, this may be applicable not only during COVID-19 pandemic in particular, but also in other situations in which health care system cannot adequately attend all patients pending on invasive procedures, and in waiting list management of interventional cardiology in general.

No significant interaction was found between DM and other clinical variables. This simplifies the indication of not cancelling ICP in patients with DM, because mortality and cardiovascular mortality was higher in patients with DM irrespectively on other clinical characteristics.

The worse outcome in patients with DM may have several reasons. First, DM is associated with an impaired systolic and diastolic left ventricular function in patients without significant coronary artery disease, and this could have a negative impact on the outcome of patients with heart failure or valvular heart disease. Second, DM patients have a procoagulant state that may increase the risk of thromboembolic events in patients pending on structural interventions. Third, the response to anti-thrombotic agents is impaired in patients with DM, and this could have a negative impact on the risk of ischemic events in patients pending on coronary interventions. Fourth, coronary artery disease is more frequent and more severe in patients with DM, including in patients with severe valvular disease, and this could have a negative prognostic impact on clinical outcome. Finally, DM predisposes to infections, and infections constitute an important cause of non-cardiovascular death in elderly cardiovascular patients.

DM had a negative impact on mortality in all type of pending ICP. DM is associated with more severe coronary stenosis, and DM is a very well known risk factor for mortality in patients with CAD.

Among patients with aortic stenosis, those with DM have a higher mortality rate. This may be partly explained by the higher frequency of some co-morbidities (e.g. renal insufficiency) and CAD, but DM also might have a direct effect on prognosis of these patients. Among patients with aortic stenosis, those with DM have a more impaired myocardial function and more severe hypertrophy. In patients with aortic valve sclerosis, insulin resistance is a powerful independent predictor of subclinical left ventricular dysfunction regardless of concomitant visceral obesity and left ventricular hypertrophy. Additionally, DM impairs coronary microvascular function in asymptomatic patients with severe aortic and non-obstructed coronary arteries. Besides these potential explanations, the cardiac mortality of DM patients awaiting a valvular procedure was unexpectedly high in a relatively short follow-up (45 days), and this novel finding warrants further research.

Other procedures apart from coronary and valvular interventions had also higher mortality in patients with DM. DM is a risk factor for mortality in patients on atrial fibrillation, and thus it is not surprising that among those pending on LAAC, mortality was higher in diabetics.

**Study limitations.**
This study has several limitations. First, the main goal of this study was to evaluate the short-term consequences of delaying or postponing invasive cardiac procedures. Because of that, clinical follow-up was restricted to only 45 days. Second, metabolic control, treatment of diabetes and type of diabetes were not collected, and therefore the potential influence of these factors could not have evaluated. Finally, some patients underwent an emergent procedure due to clinical instability. As this occurred more frequently in patients with DM, the influence of DM on mortality in our population may have been even underestimated.

**Conclusion**

Among patients in whom an elective invasive cardiac procedure is cancelled or postponed, those with DM have an especially worse clinical outcome, with higher mortality and cardiovascular mortality at short-term, irrespective of other clinical conditions. Elective invasive cardiac procedures should be prioritized in patients with diabetes.

**List Of Abbreviations**

ASD: Atrial Septal Defect.
CABG: Coronary Artery Bypass Grafting.
CAD: Coronary Artery Disease.
CCS: Canadian Cardiac Society.
COVID-19: COronaVirus Disease 2019.
DM: Diabetes.
ICP: Invasive Cardiac Procedures.
LAAC: Left Atrial Appendage Closure.
NYHA: New York Heart Association.
PCI: Percutaneous Coronary Intervention.
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2.
TAVI: Transcatheter Aortic Valve Implantation.

**Declarations**

**Ethics approval and consent to participate:**
Since this work was done during acute phase of COVID-19 pandemic, involving aspects related with the pandemic, ethics committee aproval was not required.

**Consent for publication:**

Not applicable.

**Availability of data and materials:**

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

**Competing interest:**

The authors declare that they have no competing interests.

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**Authors' contributions:**

all authors have approved the submitted versión of the manuscript, and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Each author contribution is detailed below:

- Substantial contributions to the conception: RM, JAD, JAB, APP, FS, AGB, VRQ, FJI, BGB, MV
- Design of the work: RM, JLD, RT, IAS, RR, SO, ICG, JM, SMBP
- Acquisition, analysis, and interpretation of data: RM, PS, JAC, PP, JJM, AF, EP
- Drafted the work or substantively revised it: RM, JMTH, JFD, BV, DMS, FA, EB, EP, JRR, FL, JRR, EN, EAB, RL.

**CONFLICTS OF INTEREST:**

NONE.

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