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The effect of COVID-19 vaccination on 30-day mortality after cardiac surgery — Insights from the Israel national registries

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SUMMARY

Background: We compared the effect of perioperative COVID-19, before and after vaccination, on 30-day mortality after cardiac surgery.
Methods: Data was extracted from several national registries. The study period was March 1st, 2020—March 31st, 2022.
Results: 2594 adult patients underwent cardiac surgery before the availability of a universal COVID-19 vaccine. 33 patients were diagnosed with COVID-19 prior to surgery (mean age 58.3±10.0, mean length of time 73.6±60.1 days) and 7 patients were diagnosed with COVID-19 0—14 days after surgery (age 66.4±7.6). These were compared to 4426 patients who underwent cardiac surgery after the availability of a universal vaccine: 469 patients were diagnosed with COVID-19 prior to surgery (age 62.1±10.1, length of time 175.8±158.2) and 32 patients diagnosed with COVID-19 0—14 days after surgery (age 60.8±14.5). In patients diagnosed with COVID-19 prior to surgery, there was no excess 30-day mortality either before or after vaccination (1 (3.0%) vs. 57 (2.2%), respectively, $P<0.8$, and 8 (1.7%) vs. 87 (2.2%), respectively, $P<0.5$). Patients diagnosed with COVID-19 after surgery, but before vaccination, had significantly higher 30-day mortality compared to COVID-19 negative patients (2 (28.6%) vs. 56 (2.2%) respectively, $P<0.0001$). This excess mortality disappeared after universal vaccination (1 (3.1%) vs. 94 (2.1%) respectively, $P<0.7$).
Conclusions: COVID-19, when diagnosed in the early post-operative period, was a risk factor for mortality before available vaccinations, but not after vaccination was widely available. Pre-surgery screening and post-surgical isolation is essential until vaccines are available. This data may be useful for patient management in future respiratory pandemics.

Abbreviations: AVR, Aortic valve replacement; CABG, Coronary artery bypass grafting; HEMR, Hospital electronic medical records; HMO, Health maintenance organizations; MOH, Ministry of health; MVR, Mitral valve replacement; MVr, Mitral valve repair.

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Introduction

In December 2019, a novel coronavirus (SARS-CoV-2) pandemic, also termed COVID-19, emerged, and rapidly spread across the globe, leading to extreme public health measures including widespread lockdowns. A published meta-analysis reported that increasing age and comorbidities, such as diabetes, renal failure, and cardiovascular diseases, were significant risk factors for COVID-19 [1]. Patients with pre-existing conditions who had low physiological reserve were particularly vulnerable to COVID-19 due to its effects on multiple organs, including the cardiovascular system [2]. Further studies revealed that COVID-19 also increased the risk of developing cardiovascular disorders, such as myocardial injury and myocarditis, arrhythmias, and acute coronary syndrome [3—5]. Patients scheduled for surgery were particularly at risk of COVID-19 infection and post-surgery complications. Multiple studies have examined outcomes of patients with COVID-19 during the perioperative period, reporting pulmonary complications ranging from 21.2% to 51.2%, thromboembolic events from 6.8% to 13.4%, and shock from 11% to 13.9% [6—10]. Additionally, the COVIDSurg Collaborative found that previous SARS-CoV-2s infection in oncologic surgery was associated with increased odds of pulmonary complications (10.7% vs. 3.6%) [11].

During the COVID-19 pandemic, cardiac surgical procedures were frequently delayed due to changes in resource allocation, resulting in a significant decrease in the number of cardiac surgeries [12—14].

In late February 2020, the COVID-19 pandemic reached Israel, and from March 1st, 2020, to December 22nd, 2020, the country experienced three waves of the virus before the introduction of the BioN-Tech-Pfizer mRNA-BNT-162b2 vaccine [15] on December 23rd, 2020. The vaccine requires two doses for optimal protection. An early COVID-19 disease vaccination program was launched for elderly persons and for those with comorbidities. By March 31, 2022, 89.7% of population aged 60 and above (1,371,897 of 1,529,000) had been vaccinated with at least two doses.

Considering the clinical manifestation of COVID-19 and its effect on post-operative complications, and accounting for the possibility of future pandemics, we decided to use our national registries to examine the effect of vaccination on post-operative mortality in cardiac surgery during the COVID-19 pandemic. Therefore, we analyzed the Israeli national 30-day mortality after cardiac surgery data in two periods: before and after available national vaccination.

Material and methods

Data on national cardiac surgeries were obtained from identified hospital electronic medical records (HEMR) of 13 medical centers that perform cardiac surgery in Israel. Producing and sending this data to the national cardiac surgery registry at the ministry of health (MOH) is mandatory. The data is provided with specific ICD-9 codes correlated to cardiac surgery and to comorbidities (i.e., diabetes, hypertension, etc.).

Data on confirmed COVID-19 diagnoses were obtained by the auspices of the Israeli national health insurance ordinance in which it is mandatory for all four Health Maintenance Organizations (HMOs), who provide universal insurance coverage for all citizens in Israel) to report to the MOH identified data on patients with positive COVID-19 diagnosis or those that were vaccinated for Covid-19. The study was approved by the Israel MOH IRB (MHO-COR-120-2021).

All adult patients who underwent cardiac surgery in Israel between March 1st, 2020, and March 31st, 2022, were included in this study. They were divided into two periods: 1) Before universally available vaccination (March 1st, 2020, and December 22nd, 2020) 2) After universally available vaccination (December 23rd, 2020, and March 31st, 2022). Positive COVID-19 patients undergoing cardiac surgery were identified by cross—referencing the national cardiac surgery registry with the national COVID-19 registry. Thirty-day mortality data were obtained by cross-linking the patients with national Israeli social security mortality database based on national ID number. Patients' survival time was defined as the time between cardiac surgery to either date of death or date of last follow up to 30 days. Data from the national cardiac surgery registry (i.e., the number of patients who underwent cardiac surgery and data on 30-day mortality) before the pandemic was compared with data during the pandemic.

Statistical analysis

Categorical variables are presented as N (%) and chi-square analysis was used to test for statistical significance. Continuous variables are presented as mean (SD) and analyzed by a t-test (for parametric variables) or Mann Whitney U- test (for a-parametric variables). To assess the extent of survival following surgery, Kaplan-Meier curves were generated for each individual cohort. These curves were subsequently compared by log-rank test. Logistic regression was used to generate propensity score.

Finally, to produce hazard ratios of 30-day mortality we performed cox regression analysis adjusted for covariates and for propensity score which was generated by using logistic regression prior to cox regression (16) (only for significant variables). Statistical analysis was performed using the SAS package (version 9.4, SAS, Cary, NC, USA) and SPSS package (version 26). $P<0.05$ was considered statistically significant for all analyses.

Results

Population characteristics

Before universally available vaccination

The cohort consisted of 2,594 patients who underwent cardiac surgery (Table IA). They were divided into two groups: a) Thirty-three (1.3%) patients who recovered from COVID-19

Table IA
Clinical profile of the study patients (March 1st, 2020, and December 22nd, 2020, before available universal vaccination)

Variables	30-day mortality N=58	Alive N=2536
Demographics		
Age (years, mean±SD)	69.3±10.6	63.4±10.1
Gender (male)	41 (66.0%)	2036 (80.2%)
Comorbidities		
Hypertension	21 (36.2%)	1039 (41.0%)
Type 2 diabetes	22 (37.9%)	744 (29.3%)
Ischemic heart disease	37 (63.8%)	1773 (69.9%)
Dyslipidemia	21 (36.2%)	1022 (40.3%)
Atrial fibrillation	12 (20.7%)	344 (13.6%)
Obesity	6 (10.3%)	275 (10.8%)
Procedure		
CABG	29 (50.0%)	1682 (66.3%)
AVR	8 (13.8%)	383 (15.1%)
MVR	7 (12.1%)	205 (8.1%)
CABG+valve	14 (24.1%)	266 (10.5%)

before surgery and 2,561 (98.7%) patients with no COVID-19 diagnosis before surgery (Supplementary Table 1A). b) Seven (0.3%) patients with confirmed perioperative COVID-19 and 2587 (99.7%) patients with no COVID-19 (Supplementary Table 1B). Thirty-day mortality after cardiac surgery was not significantly different from the period before the COVID-19 pandemic and after the start of the pandemic ($P<0.8$, Supplementary Table 2). Sociodemographic data and the clinical profile of the patients of this period is summarized in Table IA and in supplementary Table 1A. The average age was 69.3 ±10.6, and 80.1% were males. Mean length of time between diagnosis of COVID-19 and surgery was 73.6±60.1 days (with 97% of patients diagnosed more than 14 days before surgery). The four surgical procedures that were included in the study were isolated coronary artery bypass grafting (CABG, 66.0% (1711)), isolated aortic valve replacement or repair (AVR, 15.1% (391)), isolated mitral valve replacement or repair (MVR/MVr, 8.2% (212)), and CABG + valve related procedure (10.8% (280)). Of the patients, 29.5% had been diagnosed with diabetes mellitus and 69.8% had prior ischemic heart disease (Table IA, supplementary Table 1A, 1B). The observed 30-day mortality of COVID-19 recovered patients' surgery was similar to COVID-19 negative patients (1 (3.0%) vs. 57 (2.2%) respectively, $P<0.8$, Table III). Kaplan − Meier survival analysis confirmed our findings: survival of patients who were recovered from CVOID-19 before surgery was not significantly different from patients who had no COVID-19 before surgery (96% vs 97% respectively, $P=0.8$, Figure 1).

Table IB
Clinical profile of the study patients (December 23rd, 2020−March 31st 2022, after available universal vaccination)

Variables	30-day mortality N=95	Alive N=4331
Demographics		
Age (years, mean±SD)	68.4±9.4	63.8±10.1
Gender (male)	60 (63.2%)	3478 (80.3%)
Comorbidities		
Hypertension	32 (33.7%)	1711 (39.5%)
Type 2 diabetes	30 (31.6%)	1225 (28.3%)
Ischemic heart disease	67 (70.5%)	3070 (70.9%)
Dyslipidemia	37 (38.9%)	1775 (41.0%)
Atrial fibrillation	16 (16.8%)	548 (12.7%)
Obesity	15 (15.8%)	468 (10.8%)
Procedure		
CABG	46 (48.4%)	2896 (66.7%)
AVR	13 (13.7%)	640 (14.8%)
MVR	9 (9.5%)	340 (7.9%)
CABG+valve	27 (28.4%)	455 (10.5%)

The observed 30-day mortality of immediate post-operative COVID-19 positive patients was significantly higher compared to COVID-19 negative patients (2 (28.6%) vs. 56 (2.2%), respectively, $P<0.0001$ (Table IIA). Using Kaplan-Meier curves confirmed our findings: survival for patients who had COVID-19 from the date of surgery to 14-days after surgery was significantly lower from patients who had no positive COVID-19 (71% vs 97% respectively, $P<0.0001$, Figure 2). Propensity-adjusted survival analysis (cox regression) revealed that post-operative COVID-19 had a hazard ratio of 14.3 (95% CI 3.4−60.1) for 30-day mortality Table III.

After an available universal vaccine

The cohort consisted of 4,426 patients who underwent cardiac surgery (Table IB). They were divided into two groups: a) 469 (10.6%) patients who recovered from COVID-19 before surgery (of whom 92% of patients recovered more than 14-days before surgery) and 3,957 (89.4%) patients with no known COVID-19 before surgery (Supplementary Table 1C). b) 32 (0.7%) patients with a positive COVID-19 test in the 14-days after surgery and 4,394 (99.3%) patients with no positive COVID-19 diagnosis after surgery (Supplementary Table 1D). Thirty-day mortality after cardiac surgery, both for patients who recovered from COVID-19 before surgery and for patients with a positive COVID-19 test in the 14-days after surgery, was not significantly different before the COVID-19 pandemic and after the COVID-19 pandemic ($P<0.1$, Supplementary Table 2). The sociodemographic and clinical profile of the patients in this period is summarized in Table IB, supplementary Table 1C and 1D. The average age was 68.4±9.4, and 79.9% were males. The mean length of time between diagnosis of COVID-19 and surgery was 175.8±158.2 days. The four surgical procedures that were included were isolated CABG (66.5% (2942)), 14.8% (653) isolated AVR, 7.9% (349) isolated MVR/MVr, and 10.9% (482) CABG + valve related procedure. Of the patients, 28.4% had been diagnosed with diabetes mellitus and 70.9% had prior ischemic heart disease (Table IB and supplementary Table 1C). The observed 30-day mortality of COVID-19 recovered patients before surgery was similar to no positive COVID-19 (8 (1.7%) vs 87 (2.2%) respectively, $P<0.5$, Table IIB). Using Kaplan-Meier survival analysis confirmed our findings: survival of patients who recovered from COVID-19 prior to surgery was not significantly different from patients who were COVID-19 negative (98% vs 97% respectively, $P<0.5$, Figure 3).

The observed 30-day mortality of immediate post-operative positive COVID-19 was similar to COVID-19 negative patients (1 (3.1%) vs 94 (2.1%) respectively, $P<0.7$, Table IIB). Kaplan-Meier survival analysis confirmed our findings: the survival of patients who were positive for COVID-19 after surgery was not

Table IIA
Thirty-day mortality prior to available universal vaccination

Confirmed COVID-19 before surgery	30-day mortality	No COVID-19 before surgery	30-day mortality	P	Confirmed COVID-19 from surgery to 14 days post-op	30-day mortality	No COVID-19 from surgery to 14 days post-op	30-day mortality	P
N (%)	*N* (%)	*N* (%)	*N* (%)		*N* (%)	*N* (%)	*N* (%)	*N* (%)	
33 (1.3%)	1 (3.0%)	2561 (98.7%)	57 (2.2%)	0.8	7 (0.3%)	2 (28.6%)	2587 (99.7%)	56 (2.2%)	0.0001

Table IIB
Thirty-day mortality after available universal vaccination

Confirmed COVID-19 before surgery	30-day mortality	No COVID-19 before surgery	30-day mortality	P	Confirmed COVID-19 from surgery to 14 days post-op	30-day mortality	No COVID-19 from surgery to 14 days post-op	30-day 2mortality	P
N (%)	*N* (%)	*N* (%)	*N* (%)		*N* (%)	*N* (%)	*N* (%)	*N* (%)	
469 (10.6%)	8 (1.7%)	3957 (89.4%)	87 (2.2%)	0.5	32 (0.7%)	1 (3.1%)	4394 (99.3%)	94 (2.1%)	0.7

Table III
Propensity — adjusted survival for 30-day mortality following cardiac surgery with perioperative or postoperative COVID-19, before available vaccination (March 1st, 2020, and December 22nd, 2020)

Parameter	HR (95% CI)	*P* Value
Positive COVID-19 (vs negative COVID-19) at date of surgery to 14 days post-op	14.3 (3.4—60.1)	0.0003
Age (years)	1.1 (1.03—1.1)	0.0001
Combined CABG + valve procedure (vs CABG)	2.6 (1.4—5.0)	0.004
MVR (vs CABG)	4.2 (1.1—15.9)	0.04

CABG — isolated Coronary Artery Bypass Grafting, MVR-isolated mitral valve replacement.

significantly different from COVID-19 negative patients (96% vs 97% respectively, $P<0.7$, Figure 4).

Discussion

In this retrospective analysis of the Israeli adult cardiac surgery database these were the main findings: 1) Preoperative COVID-19 was not a risk factor for mortality either before or after vaccination. 2) Perioperative COVID-19 was a risk factor for mortality after surgery before available vaccination, but ceased being a risk factor after a vaccine became widely available. 3) For the entire cohort, there was no excess mortality during the outbreak of the pandemic, before available national vaccination, compared to the months before the pandemic.

Our findings confirm those of several studies conducted at the beginning of the COVID-19 outbreak. Studies involving general surgery patients reported a high 30-day mortality rate during the perioperative period among COVID-19-positive patients. One study [16] found that surgical patients who tested positive for COVID-19 had a two-fold higher risk of in-hospital death than patients who tested negative. Another study by Chang SH *et al.* [17] examined patients after thoracic surgery due to COVID-19 complications between March and August 2020 and found a 23% in-hospital mortality rate. Two other studies conducted by the COVIDSurg Collaborative were incongruous with our findings: One study which was conducted from March 2020 to May 2020 reported that diagnosis of COVID-19 within 4 weeks before operation (in oncologic surgery) increases the risk of 30-day mortality (11), and the other that included all patients undergoing surgery who had SARS-CoV-2 infection diagnosed within 7 days before or 30-days after surgery (between Jan and March, 2020, surgery for any indication were eligible) found that 30-day mortality among postoperative COVID-19 patients was higher than preoperative COVID-19 patients (25.6% vs. 21.2%, respectively, $P<0.0001$) [6]. Another study from Italy, in contrast to our findings [9], reported a significantly higher 30-day mortality rate for COVID-19 positive patients diagnosed pre-surgery compared to those who were negative for the virus (19.5% vs. 2.4% respectively).

Two studies examined patients with COVID-19 after cardiac surgery. A study from Brazil [18], conducted between March 2020 and July 2021, found that patients who tested positive for COVID-19 more than 10 days after surgery had a threefold higher risk of death compared to patients who were diagnosed positive for COVID-19 more than 10 days before undergoing cardiac surgery, with a mortality rate of 27.3%. Another study [19] showed that patients who developed COVID-19 infection following surgery had a significantly higher mortality rate, up to 44%, than those who tested negative. Kochi *et al.* [20] suggested that the cause of death among COVID-19 patients who underwent surgery was due to the hyperinflammatory microenvironment produced by the virus, which causes an imbalance between infection-induced increase in metabolic demand and diminished cardiorespiratory reserve.

Most of the studies examining COVID-19 related surgical complications were conducted before vaccines were available and did not focus on cardiac surgery patients. There are a few possible explanations for the discrepancies between other studies' results and our results. First, we examined a relatively long period prior to vaccination (between March and December 2020) while most studies focused on a short period, mainly at

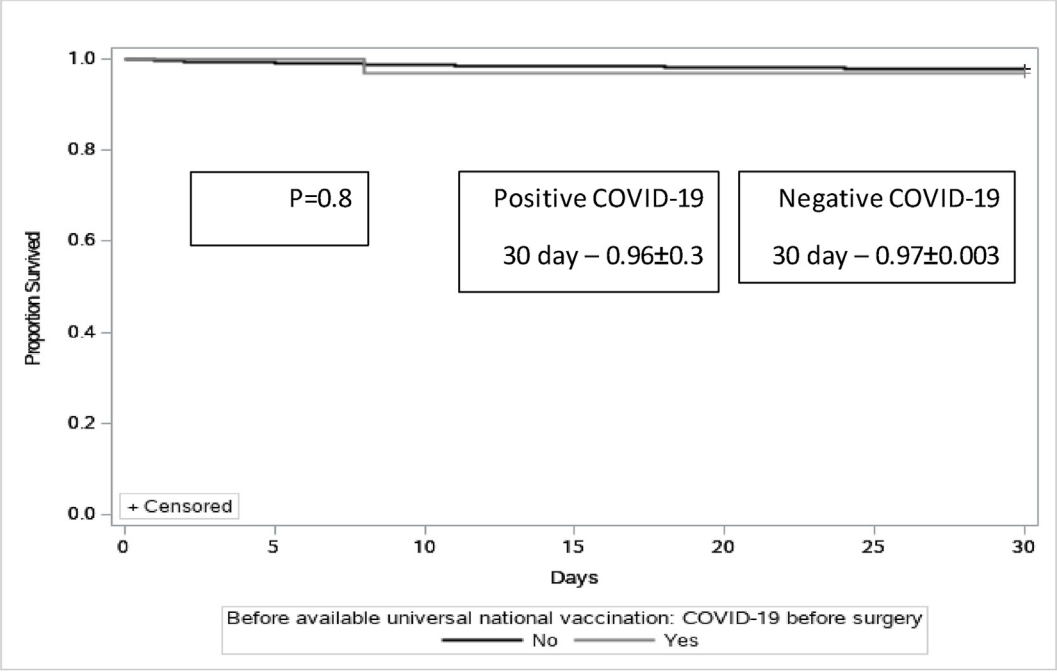

Figure 1. Kaplan-Meier survival curve for positive and negative Covid-19 before cardiac surgery, before available universal vaccination.

the beginning of the outbreak. As time went on, countries managed to obtain sufficient equipment, including mechanical ventilators, and to have improved staffing and care processes [1]. Another possible cause for the disparity is that high-income countries, as compared to mid and low-income countries, had better access to ventilators and medicines early in the pandemic. Obviously, different countries started the pandemic with different healthcare system capacities and abilities and last, another possible factor, different countries used different strategies to contain the pandemic. Several countries used a "mitigation" strategy and some a "containment" strategy and therefore there were different rates of morbidity and mortality in different countries [1].

In Israel, the COVID-19 vaccination campaign began on December 23rd, 2020, using the BNT162b2 vaccine, which has been shown to have high vaccine efficacy and effectiveness in

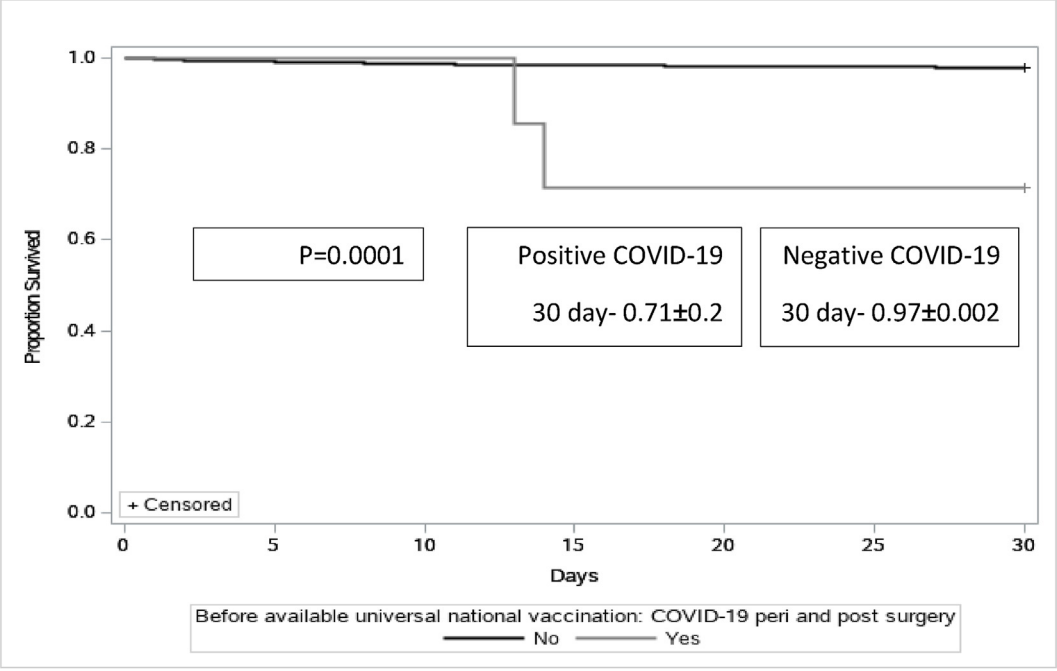

Figure 2. Kaplan-Meier survival curve for positive and negative Covid-19 in the perioperative and post - operative cardiac surgery, before available universal vaccination.

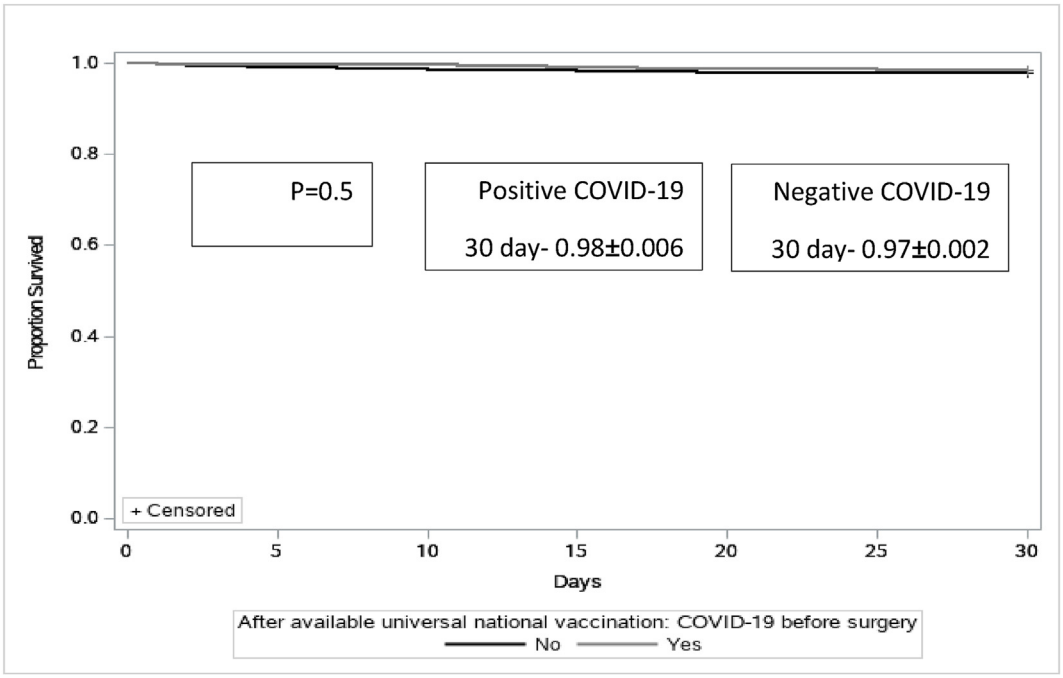

Figure 3. Kaplan-Meier survival curve for positive and negative Covid-19 before cardiac surgery, after available universal vaccination.

two-dose recipients [15,21]. On May 18th, 2021, population-level protection from the COVID-19 pandemic was apparently achieved in Israel, and the vaccine played a major role in the decline of COVID-19 infections in 2021 [21]. Our study shows that the vaccine also reduced the risk of postoperative mortality among patients with a positive COVID-19 test in the 14 days after surgery. Although, during the availability of vaccination at a national level, Israel experienced 3 different variants (between December 2020 to July 2021- Alfa variant, August 2021 to December 2021 Delta variant, and January 2022 to March 2022 the Omicron variant), it seems that the vaccine was effective in eliminating the risk of mortality in all types of COVID-19 variants.

Cardiac surgery patients require a delicate balance between the risks of delaying surgery to minimize peri- and post-operative mortality and waiting too long prior to surgery so

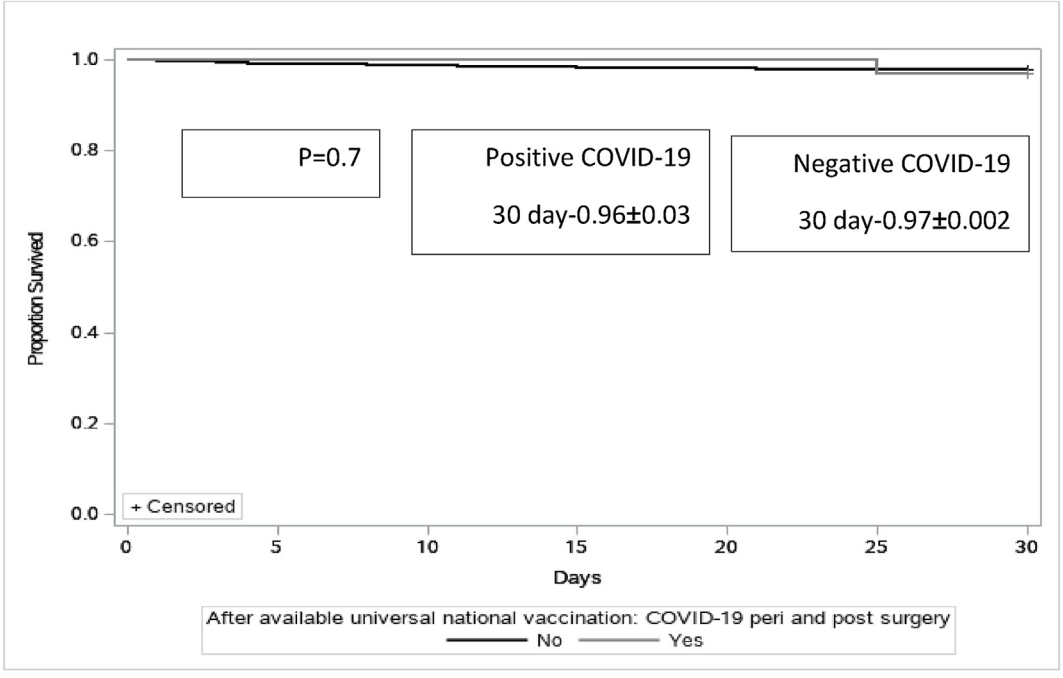

Figure 4. Kaplan-Meier survival curve for positive and negative Covid-19 in the perioperative and post-operative cardiac surgery, after available universal vaccination.

that they succumb to their cardiovascular disease. Our study found that COVID-19 infection before surgery was not associated with 30-day mortality before or after the vaccine period. However, COVID-19 infection after surgery, but before the vaccine period, was significantly associated with 30-day mortality. Based on our findings, we recommend not postponing urgent cardiac surgeries during a similar respiratory pandemic outbreak while maintaining adequate precautions according to the knowledge about the virus and its characteristics at each time point. For cardiac surgery candidates who are urgent or emergent, we propose the following:

- Before the availability of vaccines, patients who are candidates for cardiac surgery, including elective patients, should be held in relative isolation about a week before surgery and screened immediately after surgery for the virus. Urgent/emergent patients should be screened for the pandemic virus before surgery but not have their surgery postponed. While waiting for the results, prepare sterile operating rooms and post-surgery rooms and staffed settings to reduce exposures for healthcare workers and for patients who are awaiting surgery.
- After the availability of vaccines patients who are candidates for cardiac surgery, either elective or urgent, should be assessed before surgery whether they were vaccinated or not. Vaccinated patients can be operated without any delay. For unvaccinated patients, surgery should be delayed for elective patients, while for urgent patients' surgery should be performed as scheduled.

Limitations

First, Israel is considered a high-income country with access to medical resources and the means to obtain ventilators, protective equipment, medicines, and vaccinations earlier than other countries. Additionally, Israel has a public healthcare system that is accessible to all citizens. The small number of COVID-19 patients and the low 30-day mortality rate observed in our study may be attributed to the Israeli government's effective strategies in managing the outbreak. Therefore, our findings may be limited to countries with similar resources and healthcare systems. Second, we assume that some of the patients diagnosed in the first 14 days would have contracted COVID-19 in the days before surgery and maybe even at the time of surgery.

The study is retrospective and therefore prone to biases and confounding.

Conclusions

Our study underscores the importance of implementing measures to reduce the risk of COVID-19 infection after cardiac surgery, as it is associated with a higher 30-day mortality rate during an outbreak of a pandemic. Our findings suggest that pre-surgical screening and post-surgical isolation during the pre-vaccination period can help reduce the risk of infection transmission among patients. Furthermore, the availability of vaccines offers hope for reducing the risk of COVID-19-related mortality among surgical patients.

In future pandemic pandemics, with good pre-pandemic preparations, we believe it is possible to continue operating without delaying surgeries. However, pre-surgery screening and post-surgical isolation is essential until vaccines are available.

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Author contributions

O.B conceived the study idea, initiated and managed the study, interpreted the statistical data and wrote the initial draft. A.R performed the statistical analysis, M.R assisted in collecting the data, I.C and E.S revised the paper and D.L contributed to critical revision of the paper. All authors agreed to be accountable for all aspects of the work.

Conflict of interest statement

The authors report no conflicts of interest.

Ethics approval and consent to participate

This study was approved by the supreme ethical review board of Israeli Ministry of health (MOH) (approval # MHO-COR-120-2021) from January ,3, 2022. This study was conducted as part of the responsibilities of the Israel Ministry of Health.

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Appendix A. Supplementary data

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