Research Article

Impact of COVID-19 in the Age of Computer-Assisted Surgery: Cost and Effectiveness Comparison between Robotic and Minimally Invasive Mitral Valve Surgery in a Single-Center Experience

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Background. We conducted a cost and effectiveness analysis comparing robotic vs minimally invasive mitral valve surgery (RMVS vs MIMVS). The aim was to assess whether the higher cost of the robotic technique could be mitigated by the clinical advantages. Methods. We included 118 patients undergoing RMVS and 233 patients undergoing MIMVS. Initially, RMVS experience was developed during the COVID-19 pandemic. A propensity score matching analysis was performed. Postoperative outcomes and cost of care were compared. Results. RMVS patients had significantly shorter ICU and hospital lengths of stay. They also had a significantly earlier return to home. The cost of the total hospitalization and healthcare services were also significantly lower. Conclusion. Shorter hospitalization and lower cost of postoperative healthcare services may mitigate the initial investment cost to purchase and maintain the robot. These benefits are all the more relevant considering that several RMVS treatments were carried out during the COVID-19 pandemic.

1. Introduction

The first use of robotic technology in cardiac surgery dates back to 1998. Despite initial hesitation, since 2011, several studies have shown renewed interest in robotic-assisted procedures for cardiac surgery. In particular, Cerny et al. observed a 112% increase in annual robotic cardiac surgery volumes over 26 European centers, from 435 in 2016 to 923 in 2019 [1]. Improved robotic technology has played a key role in this change, as magnified visualization (10x) and articulated instruments with seven degrees of freedom of movement have optimized surgical vision and dexterity.

Mitral valve (MV) repair is one of the procedures that can benefit most from the application of robotic technology [2], for which safety, effectiveness, and advantages of the robotic approach have already been described in the literature [1–6]. In this field, the most widely used robotic system to date is the Da Vinci® surgical system (Intuitive Surgical Inc., Sunnyvale, CA).

However, despite the proven intraoperative advantages of robotic-assisted MV surgery (RMVS), the high initial investment costs of the robot, the maintenance costs, and the costs of the associated disposable instruments are currently a hotly debated issue, and many cardiology centers are...
reluctant to adopt RMVS [5]. To counterbalance the economic impact of this technique, benefits should be demonstrated in terms of lower overall hospital costs for patients treated with RMVS compared to other standardized procedures, especially to minimally invasive MV surgery (MIMVS). Improved postoperative conditions of the patient should be highlighted, with a relative reduction in postoperative and total hospital stay.

Nevertheless, only a few comparative analyses are available in the literature, and the question is still debated. The reduction in hospital stay for RMVS patients could balance the additional operative cost of the device, but this is not sufficient to make the costs lower than in the MIMVS group [7]. At the same time, Hassan et al. argued that MIMVS could provide similar advantages to RMVS but with a reduced operating cost [8].

In our study, we retrospectively compared RMVS versus MIMVS procedures in our center, i.e., Humanitas Gavazzeni Hospital, Bergamo, Italy, in terms of postoperative outcomes and cost of care. Of note, our initial experience in robotic surgery, which started in May 2019, was developed during the COVID-19 pandemic period in Bergamo, Italy, with a possible detriment of postoperative outcomes.

Our objective is to quantitatively assess whether the consistent cost of the Da Vinci® surgical system can be mitigated by a significant reduction in postoperative costs, due to the clinical benefits of this technique. Since our experience with RMVS started during the COVID-19 pandemic, the possible benefits of RVMS could be considered even more relevant.

2. Materials and Methods

2.1. Study Population. The data collected and analyzed in this study were obtained from our MV surgery database, which collects information from all adult patients treated at the Humanitas Gavazzeni Hospital, Bergamo, Italy. We considered in the study patients who underwent RMVS or MIMVS between March 2014 and September 2022. More specifically, we included in this study all patients with MV dysfunction (regurgitation or stenosis), regardless of etiology. All surgical techniques (different types of MV repair or replacement), all cross-aortic clamp techniques (external or endoaortic), and procedures combined with mitral surgery were included. Patients with coronary artery disease were excluded. A total of 351 patients were included: 233 patients underwent MIMVS and 118 patients underwent RMVS with the Da Vinci® X surgical system starting from May 2019.

The patients underwent a preoperative diagnostic workup, if not performed in the preceding six months, consisting of a computed tomography (CT) scan of chest, abdomen, and pelvis, a coronary angiography, a trans-thoracic or transesophageal echocardiography, an electrocardiography, and routine biochemistry. In the postoperative period, all patients underwent regular examinations according to the postoperative course: biochemical examinations, chest X-ray, echocardiography, or CT scan.

Different postoperative management of patients was based on a collegial clinical evaluation of each patient. A fast-track protocol including rapid extubation, mobilization, and reduction of ICU length of stay was applied if the patient had specific characteristics, i.e., no bleeding, no inotropic drugs and hemodynamic stability, correct blood gas values, biochemical profile of blood tests in the normal range, and no neurological deficits.

All patients signed the informed consent for the surgical procedure. The data processed in this study were handled anonymously. Patient consent was not required for this study due to the retrospective nature of the analysis.

The study was approved by the Ethics Committee of IRCCS Clinical Institute Humanitas Rozzano, Italy (Approval Code 213/20; Date: March 10, 2020).

The cost data used in this analysis concern the postoperative period and general hospitalization. The costs of the individual healthcare services were taken from the relevant Ministerial Decree [9], while the average daily cost was extracted from a study concerning hospitalization in the Lombardy Region, Italy, where the Humanitas Gavazzeni Hospital is located [10]. For each patient, the individual costs were multiplied by the amount of services required.

2.2. Surgical Techniques. The adopted MIMVS technique has been previously described, with optimal clinical results [11, 12]. Briefly, minithoracotomy access is achieved with an incision of 4–6 cm in the fourth or third intercostal space (working port). A second port is adopted to introduce video assistance, i.e., the Endocamaleon camera (Karl Storz Inc., Tuttlingen, Germany). Cardiotomy aspiration and carbon dioxide insufflation are performed via a third port. Cardiopulmonary bypass (CPB) is established peripherally by arterial and femoral cannulation. An external aortic cross-clamp (Chitwood or Cygnet) or the IntraClude endoaortic balloon (Edwards Lifesciences Inc., Irvine, CA, US) is adopted.

Also the adopted RMVS technique has been previously described [2]. In summary, an incision of 1.5–2 cm is performed in the third intercostal space for the working port access, and four other incisions of 0.8 cm are performed as instrumental ports (camera arm, right and left arm, and dynamic left arm). CPB and aortic cross clamp were performed in the same way as in MIMVS [2].

In most patients in both groups, we adopted the “Lavaredo Technique” and the implantation of a complete ring for mitral valve repair. This previously described approach [13, 14], which briefly consists of free-margin suturing of the mitral leaflet, has been shown to be safe and effective at follow-up and has been used indiscriminately in the MIMVS and RMVS [15].

Cold crystalloid cardioplegia (HTK solution, Custodiol, Franz Köhler Chemie GmbH, Bensheim, Germany) was used for all patients of the study.

2.3. Statistical Analysis. The analyzed continuous variables are reported as mean ± standard deviation (SD) when normally distributed (p value of the Shapiro–Wilk’s test
greater than 0.05) and as median together with 25th and 75th percentiles in square brackets otherwise. The analyzed binary variables are reported in terms of frequencies and proportions.

To compare RMVS and MIMVS, a pairwise matching procedure was used to reduce the effects of selection bias and possible confounding factors between the groups. A propensity score was derived from a logistic regression model that included the following relevant baseline preoperative characteristics, which significantly varied between RMVS and MIMVS populations (p value <0.05): age, gender, BMI, atrial fibrillation, left ventricular ejection fraction, and EUROSCORE II. Each patient was assigned a propensity score reflecting the probability of receiving RMVS. RMVS and MIMVS cases were matched by their propensity score in blocks of 1:1, thus obtaining the matched subpopulations. The propensity score and the matched groups were obtained through the IBM SPSS software (version 20; IBM Corp, Armonk, NY, USA).

Statistical comparisons between RMVS and MIMVS populations were made considering both the entire study population and the matched population. Continuous variables were compared using the two-tailed Student’s t-test when normally distributed or the two-tailed Wilcoxon rank-sum test otherwise. Binary variables were compared using the two-tailed Fisher test. Differences were considered statistically significant if the p value was less than 0.05. These tests were performed using the R software (version 4.3.0, R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Table 1(a) shows the preoperative characteristics of the whole study population. It can be seen that some of them are different between RMVS and MIMVS, which justifies the inclusion of matched groups. Table 1(b) shows preoperative characteristics of two matched groups. It can be observed that, in this case, almost all considered preoperative characteristics were similar (p-value >0.05) in the matched groups, reflecting good matching.

The combined procedures observed involved appendage, patent foramen ovale, and atrial septal defect. Their numbers were limited and, more importantly, similar between RMVS and MIMVS, both considering the overall populations and those that matched with the propensity score. Indeed, the maximum percentage of a combined procedure in a group was 12.7% of cases, while the maximum difference between RMVS and MIMVS was 8.4%.

Figure 1 shows the boxplots of the major postoperative outcomes that resulted significant between the groups, considering both the overall RMVS and MIMVS populations and the matched ones. Clamp time, reported in Figure 1(a), was significantly lower in the RMVS group, both considering the whole populations (p value = 0.019) and the matched ones (p value <0.01). This implies a decreased risk of developing cardiac ischemia for the RMVS patients. Also, postoperative intubation time, reported in Figure 1(b), was significantly lower in the RMVS group, both considering the whole populations and the matched ones (p value <0.01 in both cases). In fact, using the Da Vinci® X surgical system, it is possible to apply the fast-track extubation procedure through which the patient can be extubated directly on the operating table, without the need for mechanical ventilation during postoperative hospitalization. Specifically, 65.1% of patients in the RMVS group were extubated in the operating room, while all patients in the MIMVS group continued invasive mechanical ventilation in the ICU. Accordingly, as can be seen in Figure 1(c), postoperative ICU length of stay was significantly reduced in the RMVS patients (p value <0.01 for both whole and matched populations); this leads to a more targeted and personalized mobilization of the patient. The combination of the abovementioned factors and greater precision during the surgery led to a rapid recovery of the patient with a consequent decrease in hospital length of stay for the RMVS (p value <0.01 for both whole and matched populations), as shown in Figure 1(d), and faster psychofunctional recovery.

A summary of all postoperative outcomes considered is finally reported in Table 2(a). Among the other variables, it is worth mentioning that the percentage of patients discharged home rather than to specialized postoperative rehabilitation facilities is significantly higher for the RMVS patients (p value <0.01 both whole and matched populations), which is clearly associated with a rapid return of patients to their daily routine. As for the angiography, it was either performed once (with a cost of 632 euros) or not (with a null cost). In particular, when considering the original populations, it was not performed in 40 out of the 118 RMVS patients, and in 35 out of the 233 MIMVS patients. When considering the matched populations, it was not performed in 24 out of the 80 RMVS patients and in 15 out of the 80 MIMVS patients. This clearly shows that the populations are different and resulted in the low p values reported.

From an economic perspective, Figure 2 shows the boxplots of the cost of the total hospital stay, which was significantly lower in the RMVS group (p value <0.01 for both whole and matched populations). In fact, the average cost for a patient treated with RMVS was approximately €8,000, instead of approximately €10,000 for a patient treated with MIMVS. The reduction in costs is related to a lower number of instrumental medical tests and medical consultations in the postoperative period, as well as to a reduction in hospital and intensive care stays. For the sake of completeness, a summary of all considered cost variables is finally given in Table 2.

4. Discussion

Robotic mitral valve surgery is gaining popularity in this era with increasing use in clinical practice worldwide. The safety and efficacy of this approach have already been demonstrated [5, 16–18] in terms of morbidity, mortality, and repair success rate comparable to the minimally invasive approach.

In our study, mortality was zero in both groups. No patient underwent reoperation due to early failure, and there was no significant difference in terms of revision for bleeding. We noted a significant reduction in aortic cross-
**Table 1:** Preoperative characteristics of the whole study population, overall, and according to the type of surgery, with p value between the groups (a) and preoperative characteristics of the matched populations according to the type of surgery, with p value between the groups (b).

(a) Overall (N = 351) | RMVS (N = 118) | MIMVS (N = 233) | p value
---|---|---|---
Age (years) | 63 [52, 71] | 58 ± 13 | 64 [54, 72] | <0.01
Gender female, n (%) | 161 (44) | 38 (32) | 123 (49) | <0.01
BMI | 24.60 [22.07, 27.20] | 23.73 [21.66, 26.19] | 25.06 [22.40, 22.72] | <0.01
Atrial fibrillation, n (%) | 83 (23) | 14 (12) | 69 (28) | <0.01
Ejection fraction | 60 [56, 65] | 64 [60, 67] | 60 [55, 61] | <0.01
EUROSCORE II (pts) | 0.94 [0.69, 1.5] | 0.89 [0.67, 1.17] | 0.99 [0.70, 1.68] | <0.01

(b) Matched RMVS (n = 80) | Matched MIMVS (n = 80) | p value
---|---|---
Age (years) | 58 [50, 67] | 59 [51, 66] | 0.55
Gender female, n (%) | 26 (33) | 30 (38) | 0.62
BMI | 23 [21, 26] | 24 [22, 26] | 0.21
Atrial fibrillation, n (%) | 11 (14) | 16 (20) | 0.40
Ejection fraction | 63 [60, 68] | 60 [57, 62] | <0.01
EUROSCORE II (pts) | 0.88 [0.67, 1.12] | 0.70 [0.60, 0.99] | 0.08

GFR = glomerular filtration rate; PAPs = systolic pulmonary artery pressure.

**Figure 1:** Boxplots of major postoperative outcomes that were significant between the groups (M denotes matched RMVS or MIMVS population): clamp time (a), postoperative intubation time (b), ICU length of stay (c), and hospital length of stay (d).
### Table 2: Outcomes of the matched population according to the type of surgery for both the overall RMVS and MIMVS populations and the matched ones: clinical outcomes (a) and costs in euro (b).

<table>
<thead>
<tr>
<th></th>
<th>RMVS (N = 118)</th>
<th>MIMVS (N = 233)</th>
<th>p-value</th>
<th>Matched RMVS (N = 80)</th>
<th>Matched MIMVS (N = 80)</th>
<th>p-value</th>
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<tbody>
<tr>
<td><strong>CPB time (minutes)</strong></td>
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<td></td>
<td>165 [148.2, 183]</td>
<td>136 [122, 158]</td>
<td>&lt;0.01</td>
<td>163 [148, 182]</td>
<td>140 [123, 158]</td>
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<td><strong>Clamp time (minutes)</strong></td>
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<td>91 [82.5, 105]</td>
<td>98.5 [86; 116]</td>
<td>0.019</td>
<td>89 [80, 102]</td>
<td>100 [86, 117]</td>
<td>&lt;0.01</td>
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<td><strong>Operative time (minutes)</strong></td>
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<td></td>
<td>260 [230, 295]</td>
<td>235 [215, 260]</td>
<td>&lt;0.01</td>
<td>255 [228, 285]</td>
<td>235 [210, 263]</td>
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<td><strong>Transfused, n (%)</strong></td>
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<td>35 (29)</td>
<td>80 (32)</td>
<td>0.34</td>
<td>17 (21)</td>
<td>12 (15)</td>
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<td><strong>Postoperative intubation time (hours)</strong></td>
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<td>3 [0, 5]</td>
<td>8 [5, 13]</td>
<td>&lt;0.01</td>
<td>2 [0, 4]</td>
<td>6 [4, 12]</td>
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<td><strong>Revision for bleeding, n (%)</strong></td>
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<td>4 (3)</td>
<td>3 (4)</td>
<td>0.23</td>
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<td><strong>ICU length of stay (hours)</strong></td>
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<td>40 [20, 44]</td>
<td>45 [43, 88]</td>
<td>&lt;0.01</td>
<td>32 [20, 43]</td>
<td>45 [42, 68]</td>
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<td><strong>Hospital length of stay (days)</strong></td>
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<td>10 [9, 12]</td>
<td>11 [10, 15]</td>
<td>&lt;0.01</td>
<td>10 [9, 12]</td>
<td>11 [10, 14]</td>
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<td><strong>In-hospital death, n (%)</strong></td>
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<td>Discharge at home, n (%)</td>
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<td>&lt;0.01</td>
<td>72 (90)</td>
<td>50 (63)</td>
<td>&lt;0.01</td>
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<thead>
<tr>
<th>(b)</th>
<th>RMVS (N = 118)</th>
<th>MIMVS (N = 233)</th>
<th>p-value</th>
<th>Matched RMVS (N = 80)</th>
<th>Matched MIMVS (N = 80)</th>
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<tr>
<td><strong>Cost of total hospital stay</strong></td>
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<td>7874 [6550, 9527]</td>
<td>10433 [8819, 12744]</td>
<td>&lt;0.01</td>
<td>7612 [6568, 9147]</td>
<td>9695 [8780, 11659]</td>
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<td><strong>Cost of ICU stay</strong></td>
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<td>2812 [1389, 3038]</td>
<td>3159 [2986, 6128]</td>
<td>&lt;0.01</td>
<td>2187 [1389, 2934]</td>
<td>3125 [2916, 4687]</td>
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<td><strong>Cost of general ward stay</strong></td>
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<td>4730 [4257, 5676]</td>
<td>5203 [4730, 7095]</td>
<td>&lt;0.01</td>
<td>4730 [4257, 5676]</td>
<td>5203 [4730, 6622]</td>
<td>&lt;0.01</td>
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<td><strong>Cost for total in hospital healthcare services</strong></td>
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<td>&lt;0.01</td>
<td>2654 [2303, 3892]</td>
<td>4073 [3772, 5771]</td>
<td>&lt;0.01</td>
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<td><strong>Angiography</strong></td>
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<td>632 [0, 632]</td>
<td>632 [632, 632]</td>
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<td>632 [632, 632]</td>
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<td><strong>Chest radiography</strong></td>
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<td><strong>CT-scan</strong></td>
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<td>124 [124, 124]</td>
<td>124 [124, 124]</td>
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<td><strong>Echocardiography</strong></td>
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<td>102 [102, 102]</td>
<td>102 [102, 102]</td>
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<td><strong>Carotid ultrasonography</strong></td>
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<td>&lt;0.01</td>
<td>44 [44, 44]</td>
<td>44 [44, 44]</td>
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clamp time in the RMVS group: an explanation is that in our center, MIMVS and RAMVS are performed by expert surgeons who can further improve their performance by taking advantage of the benefits of the robotic platform in terms of high-definition three-dimensional visualization and magnification, increased surgical dexterity, and excellent precision enabled by robotic instruments.

Another observation concerns CPB and total operative times, which were lower in the MIMVS group than in the RMVS group. The main reason lies in the longer de-airing times in robotic surgery, because it is not possible to perform an effective massage of the heart directly and because the patient has a mono-lateral lung ventilation during this operation. A second reason concerns the control of bleeding sources, particularly at port insertion sites.

The important advantage of robotic-assisted cardiac surgery over conventional approaches is also the ability to reduce the size of the incision, thus limiting the operative trauma for patients. This results in less postoperative pain and, consequently, earlier mobilization and faster functional recovery. Better aesthetic outcomes improve the psychological impact on the patient and the perception of his/her disease state, with a faster return to a good quality of life. These two points are the driving forces behind robotic surgery.

However, the issues of cost containment and cost-effectiveness need to be considered. Data presented in the literature on the potential cost-effectiveness of the RMVS strategy are discordant.

Our study evaluated the postoperative outcomes and cost of care of RMVS compared with those of MIMVS to find out the possible benefits of RMVS on the patients treated in our cardiology center. Moreover, this study has an important peculiarity, as it considered the costs and benefits of an RMVS introduced only a few months before the COVID-19 outbreak in Bergamo, Italy, the second city in the world to be heavily affected after Wuhan, China. Of course, although we have previously observed a limited impact due to a well-established surgical team [19], the pandemic potentially slowed the perioperative course of patients, especially in term of postoperative hospital stay. Anyway, our analyses did not show a relevant impact on the study population.

The main finding of our analysis was that, in the context of MV disease, patients treated with RMVS through the Da Vinci® X surgical system have better postoperative outcomes, which result in lower care costs than those operated with the traditional MIMVS. Then, considering that several RMVS treatments were performed during the COVID-19 pandemic, the benefits shown in our populations are even more relevant and represent a solid lower limit of future expectations.

In particular, we observed that ICU and hospital lengths of stay were significantly lower for the RMVS patients, considering both whole and matched populations. The reason lies in early extubation, for most RMVS patients already in the operating room, early removal of invasive devices such as chest drain and bladder catheter within 24 hours, and mobilization a few hours after surgery.

This agrees with the reduction in postoperative care costs for RMVS patients reported by several authors [20–22]. Such a reduction in postoperative hospital stay is immediately reflected in a reduced need for diagnostic tests, e.g., chest x-ray, CT, echocardiography, and laboratory tests [21, 22]. As proof, in the thorough cost analysis performed by Coyan et al. based on the so-called activity-based costing, healthcare activities were calculated individually for each patient, and the RMVS group showed lower overall costs compared to the sternotomy approach [23].

Furthermore, we found that, in the RMVS group, most patients were discharged home and this was significantly different from the MIMVS group in both whole and matched populations. The lack of need for rehabilitation led to an early postoperative recovery and, consequently, a more rapid return to home, which could lead to a reduction in social costs [5, 21, 22]. Hence, improved postoperative quality of life and quicker return to home distinguished RMVS as a more effective approach [22].

Therefore, the high cost of RMVS is mitigated by the advantages of this technique, in particular the reduced invasiveness, which allows for shorter and cheaper lengths of stay, and an earlier return to home [5].

Finally, in our analysis, we intentionally did not consider the initial capital investment for purchasing the Da Vinci® X surgical system. In our hospital, this device is shared with other surgical services, especially urology and general surgery. In this way, capital and maintenance costs are borne by the different specialties and this improves the use and cost-effectiveness of the device, increasing the amortization cost per surgery [24]. However, this cost can easily be added based on each facility’s robot purchase or rental conditions, for example to determine the breakeven point.

4.1. Limitations. Some limitations of the study must be acknowledged.

(1) This cost analysis is a retrospective/observational study, with its inherent biases.
The authors declare that they have no conflicts of interest.

The observed ICU and hospital lengths of stay are obviously affected by the different postoperative management of patients, which is, however, based on a collegial clinical evaluation of patients. In this sense, the management of RMVS patients considers the reduced bleeding and postoperative pain with respect to MMVS patients, which improves chest motion and respiratory mechanics, allowing early extubation and consequently rapid mobilization.

The sample size is limited due to the single-center nature of the study and the specificity of the interventions considered. As for the COVID-19 pandemic, in addition to the impact on RMVS learning curve [19], it may also have influenced the results in subsequent years in terms of hospitalizations and length of stay, managed in such a way as to reduce contacts between patients with low bed occupancy.

5. Conclusion
The RMVS technique allows for a shorter hospital stay and earlier return to home compared to MIMVS. These clinical advantages mitigate the higher investment cost of the device and improve the cost-effectiveness of this technique. Considering the COVID-19 pandemic, the benefits shown in our RMVS population are expected to increase in the future.

Data Availability
The clinical patients data used to support the findings of this study are restricted by the IRCCS Clinical Institute Humanitas Rozzano Ethical Committee in order to protect patient privacy (PATIENT PRIVACY or ENDANGERED SPECIES). Data are available from Giroletti Laura (laura.giroletti@gmail.com) for researchers who meet the criteria for access to confidential data.

Ethical Approval
This study was approved by IRCCS Clinical Institute Humanitas Rozzano, approval code: 213/20, and approval date: March 10, 2020.

Consent
The patient’s consent to be included in the study was not necessary, due to the retrospective nature of our analysis; however, all patients signed the informed consent for the surgical procedure.

Conflicts of Interest
The authors declare that they have no conflicts of interest.

Authors’ Contributions
Laura Giroletti, Daniele Salvi, Ettore Lanzarone, and Alfonso Agnino conceptualized the study. Laura Giroletti, Daniele Salvi, Ettore Lanzarone, Valentina Grazioi, and Alfonso Agnino proposed the methodology. Valentina Grazioi, Daniele Salvi, Ettore Lanzarone, and Lorenzo Peluso provided the software. Daniele Salvi, Ettore Lanzarone, and Lorenzo Peluso were responsible for formal analysis. Daniele Salvi and Ettore Lanzarone investigated the study. Laura Giroletti, Daniele Salvi, Valentina Grazioi, and Ascanio Graniero provided the resources. Laura Giroletti, Daniele Salvi, Valentina Grazioi, and Ascanio Graniero curated the data. Laura Giroletti, Daniele Salvi, Lorenzo Peluso, and Ettore Lanzarone wrote the original draft. Laura Giroletti, Ettore Lanzarone, and Alfonso Agnino reviewed and edited the article. Laura Giroletti visualized the study. Alfonso Agnino supervised the study.

References


