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Original article

The Role of Extracorporeal Membrane Oxygenation in The Protective Lung Strategy after Cardiac Surgery in a Tertiary Intensive Care Unit

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ABSTRACT

Background: In cases of respiratory failure, Lung-Protective Ventilation Strategy (LPVS) which limits ventilator-induced lung injury is recommended. However, CO_2 retention is a major impediment for LPVS and Extracorporeal membrane oxygenation (ECMO) supplies enough time to the lungs for rest and recovery. We aimed to find out the connection between ECMO usage and the reduction of mechanical ventilatory values in patients who required ECMO therapy after cardiac surgery due to pulmonary failure.
Methods: In this retrospective cohort study, we analyzed 21 consecutive patients receiving a venovenous ECMO for pulmonary failure after cardiac surgery and 19 patients non-ECMO group. Demographic variables including age, gender, predicted body weight, and heart rate and the arterial blood gas analysis data, mechanical ventilator parameters and clinical outcomes were derived from institutional database.
Results: The mean age of the patients was 55.57 years and ECMO patients were younger than non-ECMO group patients (p=0.005). The other descriptive variables and clinical parameters did not differ between groups statistically. The mechanical ventilator parameters and arterial blood gas analysis were worse in the ECMO group before the procedure (p <0.001) whereas improvement in data was more significant in the ECMO group after the procedure (p<0.001 in Pplateau and PaO_2) . The patients in the non-ECMO group stayed longer in hospital (35.68 days vs 16.9 days) and in ICU (31.11 days vs 13.33 days) than the patients in the ECMO group. The duration of the mechanical ventilatory support did not differ between groups.
Conclusion: The intensivists had a big dilemma involving the balance between maintaining a sensible blood-gas exchange and protecting the lung from adverse effects of mechanical ventilatory support. The extracorporeal life support –ECMO- was advised until the pulmonary failure was resolved. We found that ECMO support was decreasing the high Plateau Pressure and respiratory rate more than the non-ECMO group.

1. INTRODUCTION

Here introduce the paper, and put a nomenclature if necessary, in a box with the same font size as the rest of the paper. The paragraphs continue from here and are only separated by headings, subheadings, images and formulae. The section headings are arranged by numbers, bold and 9.5 pt. Here follows further instructions for authors.
In cases of pulmonary failure and particularly in Acute Respiratory Distress Syndrome (ARDS), Lung-Protective

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Ventilation Strategy (LPVS) which suggests the usage of low tidal volume, depending on ideal body weight (IBW), and adequate levels of Positive End Expiratory Pressure (PEEP) with low threshold levels of Plateau Pressure (Pplateau), is recommended. LPVS limits not only ventilator-induced lung injury (VILI) but also concomitant biological inflammatory response [1]. Limiting tidal volume and Pplateau attested to decrease overstress on the alveoli while demanded oxygen and carbon dioxide exchange could not be met. Especially carbon dioxide retention is a major impediment for LPVS [2]. Extracorporeal membrane oxygenation (ECMO) becomes a common and lifesaver option in cases with a lower ratio of arterial oxygen tension (PaO_2) to the fraction of inspired oxygen (FiO_2) (P/F) and/or when mechanical ventilation (MV) becomes hazardous to the normal lung regions [3]. ECMO treatment could supply enough time to the lungs for rest and recovery via maintaining sufficient oxygenation and carbon dioxide elimination while refraining biotrauma, atelectotrauma and alveolar overdistension [2, 4].

There are mainly two types of ECMO, venoarterial (VA) ECMO and venovenous (VV) ECMO, and the choice usually depends on the main pathology. VA ECMO provides temporary mechanical support for both cardiac and pulmonary function while VV ECMO is usually chosen in cases of cardiovascular stability [5, 6]. The 2019 international report of the Extracorporeal Life Support Organization (ELSO) Registry showed that 59% of the adult patients receiving ECMO for severe pulmonary failure and 43% of the adult patients receiving ECMO for cardiac failure can be discharged from hospital and these ratios were getting better every year [7].

Cardiac surgery may be complicated by severe myocardial dysfunction and mild or moderate pulmonary dysfunction as in the case of ARDS or low cardiac output syndrome [8]. And in these conditions, extracorporeal life support systems like ECMO might be required. Pulmonary and chest wall mechanical properties are changed in the perioperative and postoperative period and this situation leads to muscle incoordination, reduced pulmonary compliance, and respiratory pattern change. These factors along with atelectasis and the inflammation triggered by surgery are the reasons that put forward for pulmonary failure and ARDS after cardiac surgery [9, 10]. It was reported that oxygenation and pulmonary functions were impaired after cardiac surgery in the range of 20 to 90% [11].

VV ECMO compensates the blood gas exchange in the pre-pulmonary phase and decreases mechanical ventilation dependency [5]. The limits of MV like tidal volume per ideal body weight (VT-IBW) and Pplateau could be reduced by ECMO in accordance with lung-protective ventilation strategy. This reduction extenuates the intensity and danger of VILI in theoretical [3]. However, as far as we searched through Pubmed, there is no study describing and checking if this reduction does exist in post-cardiac surgery patients. We aimed to find out the connection between ECMO usage and the reduction of mechanical ventilatory values in patients who required ECMO therapy after cardiac surgery due to ARDS or pulmonary failure.

2. METHODS

2.1. PATIENTS AND SETTINGS

In this retrospective cohort study, we analyzed all consecutive patients receiving a VV ECMO for refractory hypoxemia or hypercarbia related to ARDS or pulmonary failure after cardiac surgery between March 2016 and May 2018 in a tertiary referral state hospital. The inclusion criteria were listed below:

- Patients older than 18 years old who underwent cardiac surgery
- Patients who required VV ECMO immediately after surgery (1-72 hours) due to ARDS or pulmonary failure
- Patients who underwent ECMO therapy at least 48 hours to assess the effectivity of ECMO in LPVS

The exclusion criteria were:

- Patients who required postoperative VA ECMO support for refractory postcardiotomy cardiogenic shock and decompensated cardiomyopathy
- Any contraindication for ECMO therapy or heparin infusion
- Patients who were younger than 18 years old or older than 80 years old

As a routine procedure in our intensive care unit (ICU), prior to ECMO consideration the patients, who were troubled with pulmonary dysfunction or ARDS, were managed with LPVS consisting of sedation, neuromuscular blockade, Pplateau <35 mmHg, VT-IBW <6 ml/kg. The other parameters in the mechanical ventilator were set suitable to the patients' demands and LPVS. These data were recorded in the nurse sheet on a daily base.

Some patients recovered with this LPVS after surgery and weaned from MV support while some of them needed ECMO therapy. The recovery group was selected as the control group (the non-ECMO group) to compare the variables with the ECMO group. To overcome selection bias the ventilator and clinical parameters just before ECMO and on the third day of ECMO therapy were selected in the ECMO group, while the first day after surgery and the day before extubation (pre-weaning) were selected for the control group.

This study was categorized as a case-control study with its retrospective nature and only data from the hospital database or nurse sheets were utilized. Additional tests or data were not required for this study and an extra formal consent was not needed. We did not apply the ethics committee because our study was categorized in the non-interventional clinical research group. This study adhered to the principles in accordance with the Helsinki Declaration of 1975, as revised in 2008.

2.2. MANAGEMENTS OF ADULT VV-ECMO

In our institute, the ECMO team strictly follows the guidelines and the indications and contraindications of ECMO were described in our previous study [6]. The patients were weaned from ECMO support when the respiratory functions were improved and hemodynamic stability was accomplished with decreased need. LPVS became sufficient to accomplish desired levels of oxygenation and carbon dioxide before the removal of the ECMO support.

2.3. STATISTICAL ANALYSIS

Gathered data were transferred into Microsoft Excel Sheet and MedCalc 15.8 software (MedCalc, Ostend, Belgium) was used for statistical analysis. The nominal variables were declared as total number and percentages while the continuous variables were declared as mean ± standard deviation (SD). One-Sample Kolmogorov-Smirnov test was utilized to detect normal distribution of all data and variables, and it demonstrated that our study variables were not distributed normally. So we had to choose non-parametric statistical tests to evaluate the significance of correlations (Spearman's Rho test and Mann-Whitney U test). 2-tailed asymp. Sig. levels (p-value) ≤0.05 was regarded as statistically significant.

2.4. DATA ACQUISITION

Demographic variables including age, gender, predicted body weight, body mass index (BMI), surgical procedure, comorbidities and clinical parameters like Acute Physiology and Chronic Health Evaluation (APACHE) 2 score, Mean Arterial Pressure (MAP) and heart rate were derived from institutional database and ICU nurse sheets. The arterial blood gas analysis data, mechanical ventilator parameters and clinical outcomes like mortality, weaning, and length of stay (LOS) in ICU were derived in the same manner. After gathering all data the change of the variables in the timeline, which was explained in the patient and setting section, was calculated as follows:

Delta value of X =

$$\frac{value\ of\ X\ after\ management - value\ of\ X\ before\ management}{value\ of\ X\ before\ management} x100$$

3. RESULTS

During the study period, March 2016 and May 2018, 74 patients were identified from the database that was complicated with pulmonary failure or ARDS after cardiac surgery and admitted to our ICU. As shown in the flowchart (Figure 1), 31 of them were managed successfully with LPVS while 43 of them required ECMO therapy. The patients who required VA ECMO due to hemodynamic instability (n=22) were excluded from the study and 19 patients out of 31 LPVS success group was selected randomly -from the list in the single row- to counterbalance ECMO group.

The descriptive and clinical variables of the 40 enrolled patients were summarized in Table 1. The mean age of the patients was 55.5±14.5 years (minimum 18 and maximum 80 years old) and ECMO patients were younger than non-ECMO group patients (p=0.005). The other descriptive variables and clinical parameters like gender and comorbidities did not differ between groups statistically. Most of the patients were male (n=26, 65%) and the mean predicted body weight was 72.63±5.1 kg. Coronary Artery Bypass Grafting (CABG) was the predominant surgical procedure (n=30, 75%) while the mean APACHE 2 score was 14.6±5. 9.

The mechanical ventilator parameters and arterial blood gas analysis were described in Table 2 lengthily. These

Table 1. Descriptive and clinical variables of the groups

Variable		ECMO Group (n=21)	Non-ECMO group (n=19)	Total (n=40)	P value
Age (year)		49.7±14.5	62.0±11.6	55.5±14.5	0.005
Male gender		15 (71.4%)	11 (57.9%)	26 (65%)	0.383
Predicted body weight (kg)		72.4±5.1	72.8±5.3	72.6±5.1	0.773
Body mass index (kg/m2)		25.6±1.8	25.8±1.8	25.7±1.8	0.773
Comorbidities	HT/CHF	15 (71.4%)	13 (68.4%)	28 (70%)	0.867
	COPD	5 (23.8%)	5 (26.3%)	10 (25%)	
	CRF	1 (4.8%)	1 (5.3%)	2 (5%)	
Surgical procedure	CABG	14 (66.7%)	16 (84.2%)	30 (75%)	0.211
	Valvular pathology	7 (33.3%)	3 (15.8%)	10 (25%)	
	CABG	14 (66.7%)	16 (84.2%)	30 (75%)	
APACHE II score		14.7±5.6	14.4±6.4	14.6±5. 9	0.881
MAP (mmHg)		65.1±5.6	68.9±10.0	66.9±8.1	0.228
Heart rate (bpm)		92.6±10.9	91.6±11	92.1±10.8	0.733

Data were presented either as mean ± standard deviation or n (%). ECMO: Extracorporeal membrane oxygenation; HT: Hypertension; CHF: Congestive Heart Failure; COPD: Chronic Obstructive Pulmonary Disease; CRF: Chronic Renal Failure; CABG: Coronary Artery Bypass Grafting; APACHE 2: Acute Physiology and Chronic Health Evaluation 2; MAP: Mean Arterial Pressure.

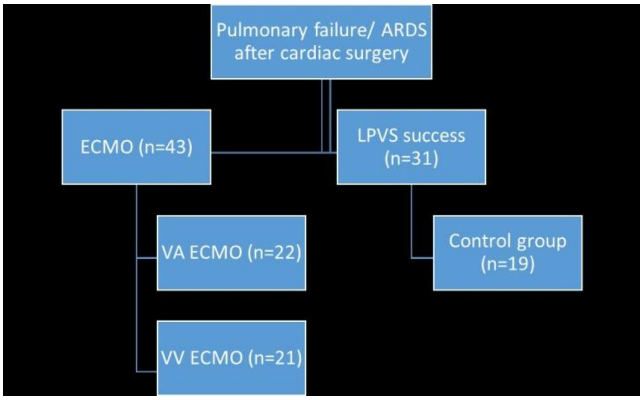

Figure 1: *The flowchart of the study population which was composed of VV ECMO and control groups. ARDS: Acute Respiratory Distress Syndrome; ECMO: Extracorporeal Membrane Oxygenation; LPVS: Lung-Protective Ventilation Strategy; VA: Venoarterial; VV: Venovenous.*

variables were worse in the ECMO group before the procedure (just before ECMO or the first day after surgery) whereas improvement in data was more significant in the ECMO group after the procedure (on the third day after ECMO or the day before extubation). The arterial blood gas analyses and the change after ECMO were significant statistically in the ECMO group. The ratio of the paO_2 to the FiO_2 (mmHg) was 91.2±37.2 before ECMO (in the ECMO group) and 196.3±16.2 after surgery (in the non-ECMO group) (p=<0.001), while it was 286.8±83.1 after ECMO (in the ECMO group) and 273.3±33.1 before weaning (the non-ECMO group) (p= 0.978). The same change was observed in Pplateau (cmH_2O) level as well; 31.2±2.6 vs. 23.4±2.4 and 15.5±2.1 vs. 19.2±2.6 (p<0.001). The difference in the $PaCO_2$ and tidal volume was not differed between groups statistically (p=0.672 and 0.456) after the procedure. The same finding could be stated for the blood lactate level. 6.1±5.6 (mmol/L) and 2.0±0.5 (mmol/L) were detected before ECMO and after surgery respectively (p=0.003). The difference was significant statistically after the procedure (either ECMO or weaning) for the blood lactate level (p=0.013). Yet, the delta level of blood lactate did not differ between groups statistically (-50.9±34.7 vs. -54.2±27.6) (p=0.797).

The change in the mechanical ventilator parameters which was demonstrated in Figure 2 was remarkable in the ECMO group and bigger than the non-ECMO group. Delta respiratory rate, delta PEEP, and delta Pplateau were decreased after ECMO more than the non-ECMO group. Delta respiratory rate was -32.5±8.7 vs. -8.7±10.4 (p<0.001) and delta PEEP was -34.7±7.7 vs. -16.6±0.3 respectively (p<0.001). Also, the difference between groups according to delta Pplateau (-49.7±8.2 vs. -17.9±6.9) (p<0.001) and delta measured tidal volume per predicted body weight (-17.6±6.0 vs. -0.8±2.6) (p<0.001) was significant statistically.

In Table 3, the outcomes of the study population were summarized. The tracheostomy rate of the study population was 27.5% (n=11) and the in-hospital mortality rate was 71.4% (n=15) in the ECMO group and much bigger than in the non-ECMO group (n=3, 15.8%) (p<0.001). This discrepancy was reflected in the length of stay (LOS) in the hospital and ICU. The patients in the non-ECMO group stayed longer in hospital (35.6±21.3 days vs. 16.9±11.1 days) (p=0.002) and in ICU (31.1±21.1days vs. 13.3±10.5 days) (p=0.003) than the patients in the ECMO group. The duration of the MV support did not differ between groups (8.3±3.7 vs. 11.1±9.0 days) respectively (p=0.724).

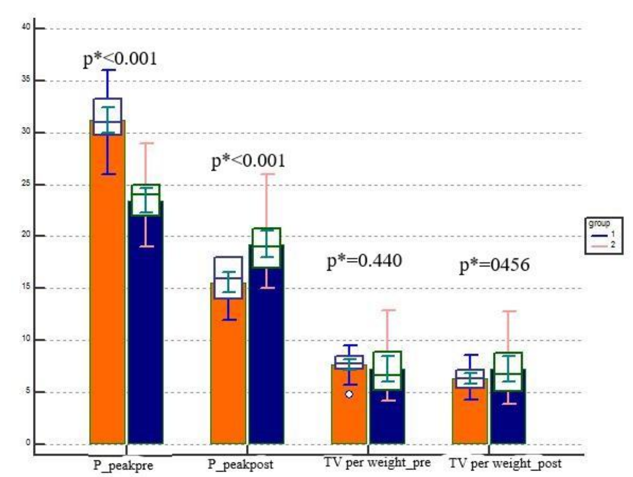

Figure 2: *The changes of the plateau pressure and tidal volume per predicted body weight (ml/kg) in the ECMO and non-ECMO groups were compared.*
Group 1 was representing ECMO group while group 2 was representing non-ECMO group.
ECMO: Extracorporeal membrane oxygenation; P_peakpre: plateau pressure just before ECMO/after surgery; P_peakpost: plateau pressure in the third day after ECMO/the day before extubation; TV per weight_pre: tidal volume per predicted body weight (ml/kg) just before ECMO/after surgery; TV per weight_post: tidal volume per predicted body weight (ml/kg) in the third day after ECMO/the day before extubation.

4. DISCUSSION

Post-op cardiac surgery may be complicated with pulmonary failure leading to high morbidity and mortality rates. Various studies declared different rates of ARDS ranging from 1.32 to 2.56 while oxygenation impairment and decreased P/F with pulmonary failure were reported in 9.1% of patients [9]. Postoperative increased shunt, atelectasis, pulmonary mechanics changes, and pulmonary endothelial injury, as well as left ventricular dysfunction, were related to the low P/F after cardiac surgery [10].

There are still debates about the timing of ECMO in cases of pulmonary failure but two major conditions are accepted widely. The first one is the need for ECMO when the MV becomes hazardous due to increment in Pplateu in spite of maneuvers like usage of neuromuscular agents, prone positioning and high PEEP to optimize ARDS management [4]. The second condition is the most argued title that consists of the P/F and some authors claimed the threshold value as 100 [3], while Papazian et al. [12] concluded that the threshold is 80 for ECMO therapy. Wu et al. [3] concluded that loosening the cut-off value of P/F to 150 would be effective to increase survival after ECMO. In our study, the mean value of P/F was 91.2 before ECMO therapy in the ECMO group, while it was detected as 196.3 in the non-ECMO group after surgery.

The intensivists had a big dilemma involving the balance between maintaining a sensible blood-gas exchange and protecting the lung from adverse effects of MV support. The efficacy of LPVS was proved repetitively in different studies and if the patient could not be ventilated with LPVS, the extracorporeal life support devices like ECMO were advised until the pathology was resolved [1, 2]. To achieve efficient oxygenation and decarboxylation, ECMO therapy claimed to be decreasing the need for high tidal volume and high Pplateu which in turn may cause progressive alveolar damage [13, 14]. In particular patients with ARDS and pulmonary failure have a decreased amount of normal alveoli that must be protected through LPVS [3]. Hence the performance of ECMO therapy in these cases is determined by the reduction in clinical and ventilator parameters like tidal volume and respiratory rate [13]. But this association was not clarified in cases of ARDS or pulmonary failure after cardiac surgery [15]. We

Table 2. Mechanical ventilator parameters and arterial blood gas analysis of groups

Variable	ECMO Group (n=21)	Non-ECMO group (n=19)	Total (n=40)	P value
Just before procedure				
Respiratory rate(bpm)	40.9±4.6	20.7±6.7	31.3±11.6	<0.001
PaO2(mmHg)	61.6±12.6	88.4±9.7	74.4± 17.5	<0.001
FIO2(%)	71.9±11.8	45.1±3.9	59.1± 16.2	<0.001
P/F (mmHg)	91.2±37.2	196.3±16.2	141.1±60.4	<0.001
Pplateau (cmH2O)	31.2±2.6	23.4±2.4	27.5±4.6	<0.001
PEEP (cmH2O)	7.6±1.5	6.0±0.5	6.8 ± 1.3	<0.001
Measured tidal volume per predicted body weight (ml/kg)	7.6±1.1	7.3±2.5	7.5±1.9	0.440
Tidal volume (mL)	554.7±74.6	525.8±171.3	541.0±128.9	0.278
pH	7.20±0.1	7.38±0.1	7.28± 0.1	<0.001
PaCO2(mmHg)	46.9±12.4	39.2±6.3	43.2±10.6	0.042
Lactate (mmol/L)	6.1±5.6	2.0±0.5	4.1±4.5	0.003
After the procedure[1]				
Respiratory rate (bpm)	27.5±4.4	19.1±7.0	23.5±7.1	0.001
PaO2 (mmHg)	134.2±28.2	103.1±15.7	119.5± 27.7	<0.001
FIO2(%)	48.3±8.4	37.8±4.8	43.3± 8.6	<0.001
P/F (mmHg)	286.8±83.1	273.3±33.1	280.4±64.0	0.978
Pplateau (cmH2O)	15.5±2.1	19.2±2.6	17.3±3.0	<0.001
PEEP (cmH2O)	5.0±1.1	5.0±0.4	5.0 ± 0.8	0.773
Measured tidal volume per predicted body weight (ml/kg)	6.3±1.0	7.2±2.5	6.7±1.9	0.456
Tidal volume (mL)	455.7±62.4	522.7±172.9	487.5±130.2	0.189
pH	7.34±0.1	7.42±0.1	7.38 ± 0.1	0.002
PaCO2 (mmHg)	31.9±5.4	31.0±4.8	31.5±5.1	0.672
Lactate (mmol/L)	3.3±5.9	0.8±0.4	2.1±4.4	0.013
Delta values of each variables				
Delta Measured tidal volume per predicted body weight	-17.6±6.0	-0.8±2.6	-9.6±9.6	<0.001
Delta Respiratory rate	-32.5±8.7	-8.7±10.4	-21.2±15.3	<0.001
Delta P/F	239.1±108.1	39.5±16.5	144.3±127.7	<0.001
Delta PEEP	-34.7±7.7	-16.6±0.25	-26.1±10.7	<0.001
Delta lactate	-50.9±34.7	-54.2±27.6	-52.5±31.2	0.797

Data were presented either as mean ± standard deviation. [1]: just before ECMO and on the third day after ECMO was selected in the ECMO group, while the first day after surgery and the day before extubation were selected for control group.
ECMO: Extracorporeal membrane oxygenation; PaO_2: Arterial Oxygen Tension; FiO_2: Fraction of Inspired Oxygen; P/F; P/F: the ratio of arterial oxygen tension to the fraction of inspired oxygen; Pplateau; plateau pressure: PEEP: Positive end expiratory pressure; $paCO_2$: Partial pressure of carbon dioxide.

Table 3. ECMO and non-ECMO groups mortality rates and outcomes				
Variable	**ECMO Group (n=21)**	**Non-ECMO group (n=19)**	**Total (n=40)**	**P value**
Weaning rate	7 (33.3%)	14 (73.7%)	21(52.5%)	0.010
Tracheostomy rate	7 (33.3%)	4 (21.1%)	11 (27.5%)	0.398
Mortality rate	15 (71.4%)	3 (15.8%)	18 (45%)	<0.001
Duration MV (days)	11.1±9.0	8.3±3.7	9.8±7.1	0.724
LOS ICU (days)	13.3±10.5	31.1±21.1	21.7±18.5	0.003
LOS hospital (days)	16.9±11.1	35.6±21.3	25.8±19.1	0.002

Data were presented either as mean ± standard deviation. ECMO: Extracorporeal membrane oxygenation; MV: Mechanical ventilation; LOS: Length of stay; ICU: Intensive care unit.

investigated this relation by composing a control group with weaning ready mechanical ventilation dependent post-cardiac surgery patients. We did explore this relationship and found that the ECMO support was decreasing the high Pplateau and respiratory rate more than the non-ECMO group. We should emphasize how we created the control group again. LPVS was successful in some patients with pulmonary failure after cardiac surgery and extubated with recovery and these patients were composing the control group. The ECMO effect was compared with this LPVS success group and more valuable with this aspect.

In this study, only the patients who underwent VV ECMO were evaluated to reckon without the possibility of pump failure and hemodynamic instability. In these cases involving cardiac failure, VA-ECMO was utilized for management.

5. CONCLUSION

ECMO support gives an opportunity for intensivists to rest or to heal damaged lung parenchyma via protective and sometimes ultra-protective ventilation.

6. LIMITATIONS

There were some limitations that we have to admit in this study. The first and the major limitation was retrospective nature which might be raising doubts about the accurate collection of patients' data. We believe that the requirement of close monitoring of the patients after cardiac surgery and ECMO therapy provides sufficient assurance about the collection of data. The second limitation was the small sample size of the study groups. We set the control group with a random selection as described in the method section to overcome selection bias.

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