The influence of metabolic syndrome in heart valve intervention. A multi-centric study.

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September 15, 2022

Abstract

Background. The effect of metabolic syndrome (MetS), defined as insulin resistance along with two or more of: obesity, atherogenic dyslipidaemia and elevated blood pressure, on post-operative complications after isolated heart valve intervention remains controversial. We hypothesized that MetS may negatively influence the post-operative course in these patients. **Methods.** Patients from 10 cardiac units who underwent isolated valve intervention (mitral ± tricuspid repair/replacement (MVS) or aortic valve replacement (SAVR), or transcatheter aortic valve replacement (TAVR) were included. MetS was defined according to the WHO criteria. Primary outcome was in-hospital mortality and overall post-operative length of stay. Relevant post-operative complications were also recorded. **Results.** From 2010 to 2019, 17283 patients underwent valve intervention. The MVS, SVAR and TAVR accounted for the 39.4%, 48.2% and 12.3% respectively of the whole. MetS compared to no-MetS was associated to higher mortality in the MVS group (6.5% vs. 2%, p<0.001), but not in the SAVR and TAVR group. In both surgical cohorts, MetS was associated with increased complications including red blood cells transfusion, renal failure, mechanical ventilation time, intensive care and overall post-operative length of stay (11 (9) vs. 10 (6), p<0.001 and 10 (6) vs. 10 (5) days, p=0.002, MVS and SAVR)). No differences were found in the TAVR cohort, with similar mortality and complications. **Conclusion.** MetS was associated to more post-operative complications, with higher mortality in the MVS group. In the TAVR cohort, post-operative complications and mortality rate did not differ between patients with and without MetS, however length of stay was longer in the MetS group.

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These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed intereptation.

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Word count : 3333

Funding: This study was supported by the British Heart Foundation and the NIHR Biomedical Research Centre at University Hospitals Bristol and Weston NHS Foundation Trust and the University of Bristol.

Conflict of interest: none declared

Data availability statement: The data that support the findings of this study are available on request from the corresponding author.

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Conclusion. MetS was associated to more post-operative complications, with higher mortality in the MVS group. In the TAVR cohort, post-operative complications and mortality rate did not differ between patients with and without MetS, however length of stay was longer in the MetS group.

Key words : Metabolic syndrome, isolated surgical heart valve intervention, transcatheter aortic valve replacement.

Glossary

BMI= Body mass index

CABG= Coronary artery bypass grafting

ICU= Intensive care unit

LOS= Length of stay

MetS= Metabolic syndrome

MHO= Metabolically healthy obese

MVS= Mitral valve surgery

RBC= Red blood cell

SAVR= Surgical aortic valve replacement

TAVR= Transcatheter aortic valve replacement

WHO= World Health Organization (WHO)

INTRODUCTION

Metabolic syndrome (MetS) is a complex condition defined by the presence of specific risk factors such as high systemic blood pressure, atherogenic dyslipidaemia, high fasting glucose concentration, and obesity(1-3). It has a high prevalence worldwide and is very prominent in countries with Western life-style, affecting around 34–39% of the adult population(4).

MetS is known to be associated to a pro-inflammatory and prothrombotic state, due to adipose tissue dysfunction and insulin resistance, with potentially harmful secretion concentration of cytokines and ultimately endothelial dysfunction(5).

Some studies have evaluated the effect of MetS on the prognosis of patients with coronary artery disease undergoing coronary artery bypass grafting (CABG)(6, 7). In a Canadian large retrospective analysis, the presence of MetS tripled the risk of in-hospital mortality after CABG(8). It appeared also, according to other studies, that patients with MetS were more prone to develop post-operative renal failure(8), or to have higher incidence of wound dehiscence(6, 8), post-operative stroke(9) and cognitive dysfunction(10).

MetS was also found to be responsible for prolonged postoperative hospital and intensive care unit stays (ICU) with women having higher stays and rates of in-hospital death (11).

The effect of MetS on post-operative complications after isolated valve intervention is poorly investigated. We hypothesized that MetS may be a detrimental condition for patients undergoing valve intervention.

Thus, the main study aim was to determine whether patients with MetS (defined according to the World Health Organization (WHO) criteria) requiring isolated valvular intervention (defined as isolated surgical aortic valve replacement (SAVR) or percutaneous aortic valve replacement (TAVR) or mitral valve surgery (repair/replacement with or without tricuspid valve repair (MVS)) were exposed to increase post-operative in-hospital mortality and prolonged post-operative length of stay (LOS). Predictors for in-hospital mortality and post-operative LOS were also examined. In-hospital survival probability and in between centres variability was investigated.

METHODS

Ethical statement

All patients provided written informed consent for the clinical and administrative storage of medical data. Given the observational nature of this study, the local ethics committee waived the need for patients' consent to analyse the data from the registry.

Study design

This was a multicentric retrospective analysis of prospectively collected data from 10 cardiac units in Italy (December 2010 to December 2019), based upon a predefined and anonymized extraction sheet. All centres entered cardiac surgery-related data into a common registry that was subject to review by a centralized clinical governance unit who checked data for accuracy and completeness monthly.

. Patients undergoing elective, urgent or emergent isolated valve intervention (MVS or SAVR or TAVR) were included in the analysis. Patients with concomitant coronary artery disease necessitating surgical or percutaneous revascularization were excluded. For the surgical strata, both standard sternotomy and minimally invasive approach were included.

Centre specification and inclusion / exclusion criteria are given in**Supplementary Material** .

Metabolic syndrome definition

There are three main definitions of MetS used for surveys and health care plan and those are the WHO of 1999, the National Cholesterol Education Program (NCEP/ATP 3) of 2005, and the International Diabetes Federation (IDF) of 2006 and are reviewed in **Supplementary Material** (2, 12).

In this study, we followed the WHO definition of MetS and we included patients with insulin resistance along with two or more of the following a) atherogenic dyslipidaemia (HDL cholesterol $<$ 0.9 mmol/L (35 mg/dl) in men, $<$ 1.0 mmol/L (40 mg/dl) in women) b) Triglycerides $>$ 1.7 mmol/L (150 mg/dl) c) Body mass index (BMI) $>$ 30 kg/m^2 d) Blood pressure $>$ 140/90 mmHg (2).

Outcomes measured

Primary outcome was in-hospital mortality (all causes) and overall post-operative LOS.

Secondary outcomes included: mechanical ventilation time and intensive care unit (ICU) stays (for the surgical cohorts only), post-operative renal failure (defined as increase in serum creatinine of more than 1.5X over seven-day duration), disabling stroke and need for red blood cells transfusion (RBC) (2 or more units of red blood cell transfused). Independent predictors associated to in-hospital mortality and post-operative LOS were investigated.

For the overall MetS and no-MetS group, in hospital survival probability and in between centres variability was also explored.

Statistical analysis

Data distributions were checked for normality before further analysis with the Shapiro–Wilk test. Continuous data are presented as the mean and standard deviation (SD) or median and interquartile range (IQR). Unpaired t-tests or Wilcoxon rank sum tests were used for statistical comparisons. Categorical data are presented as proportions and were compared using the chi-squared tests.

A generalized linear model (logit model) and linear model was used to assess the effect of multiple variables on in hospital mortality and post-operative LOS. Candidate explanatory variables (n=10) included were: MetS/no-MetS, age, sex, left ventricle ejection fraction (LVEF), renal failure, chronic obstructive pulmonary disease (COPD), redo surgery, atrial fibrillation (AF), peripheral vascular disease and previously treated coronary artery disease. In order to examine the effect of MetS stratified for each of the cohort of treatments (MVS, SAVR and TAVR), interaction term was added to the model (MetS*Treatment), keeping mitral intervention as reference level.

Linearity assumptions were checked (cran.r-project.org/web/packages=sjPlot).

As sensitivity analysis, regression model was also built including the risk factors incorporated in the MetS definition such as: BMI$>$30 kg/m^2 and as continuous variable, systemic hypertension, atherogenic dyslipidaemia and insulin resistance.

The models were also tested for multicollinearity with variance inflation factor (VIF), and explanatory variables with VIF higher than 5 were excluded since considered poor regression estimates (cran.r-project.org/web/packages=VIF). Results were presented as adjusted Odds Ratio (adj. OR) and beta-coefficients and 95% confidence intervals (Cis) (models diagnostic in **Supplementary Material**).

30-, 60- , 90- and 120-days in hospital-survival probability was also analysed using the Kaplan-Meier and corresponding survival curves were built by plotting all observations. Comparisons of survival estimates for two different patient strata (overall MetS vs. no-MetS) were performed with the log-rank statistic

In between centres mortality variability was also evaluated and pooled mortality proportion (overall MetS vs. no-MetS) plotted along with the prediction interval using a random effects model (cran.r-project.org/web/packages=meta).

All statistical analyses were performed with RStudio Team (2020) (RStudio: Integrated Development for R. RStudio, PBC, Boston, MA, USA.

RESULTS

A total of 17283 patients underwent isolated valve intervention during the study period; of these 1376 (7.9%) had clinical and laboratory findings for MetS. Overall population baseline characteristics and post-operative results for those with or without MetS are reported in**Supplementary Table 1** and **2** .

The MVS, SVAR and TAVR cohort accounted for the 39.4%, 48.2% and 12.3% of the whole cohort respectively.

Mitral ± tricuspid valve surgical cohort

Baseline patients' characteristic and post-operative results for MVS cohort (n=6815) are given in **Table 1.**

Patients in the MetS group (n=309), when compared to the no-MetS (n=6506) were older (70.8 (8.3) y/o vs. 65.2 (12.7) y/o, p<0.001), with higher proportion of female patient (57% vs. 49.1%, p=0.008), and with generally greater burdens of clinical comorbidities.

Notably, there was no difference in terms of proportion of patients operated with minimally invasive approach among the two groups (52.8% vs. 48.9%, p=0.20). Cardiopulmonary bypass (88 (46) min vs. 81 (43.5) min, p=0.37) was longer in the MetS group.

The presence of MetS was associated to increased number of patients who received at least two units of RBC (42.7% vs. 26.9%, p<0.001) and post-operative renal failure (20.1% vs. 5.9%, p<0.001). Both mechanical ventilation time (8 (7) hours vs. 7 (6) hours, p=0.02) and intensive care unit (ICU) stays (2 (2) days vs. 2 (1) days, p<0.001)) were longer in the MetS group.

Overall post-operative LOS (11 (9) days vs. 10 (6) days, p<0.001) were longer in the MetS group (**Figure 1 A/B/C**). In-hospital mortality rate was significantly higher in the MetS group (6.5% vs. 2%, p<0.001).

Surgical aortic valve replacement cohort

Baseline patients' characteristic and post-operative results for SAVR cohort (n=8340) are given in **Table 2.** Similar to the mitral cohort, patients in the MetS group (n=887), when compared to the no-MetS (n=7453) were older, with higher proportion of female sex and with greater burdens of comorbidities.

There was no difference in term of proportion of patients operated with minimally invasive approach (47.2% vs. 51.1%, p=0.20). Both cardiopulmonary bypass (79 (33) min vs. 75 (35) min, p=0.005) and cross clamp time (62 (27) min vs. 60 (28) min, p=0.07) were longer in the MetS than in the no-MetS.

Mets group, compared to no-MetS, had increased number of patients who received at least two units of RBC (40.2% vs. 27.7%, p<0.001) and experienced post-operative renal failure (10.1% vs. 5.6%, p<0.001). ICU stay (2 (2) days vs. 2 (1) days, p=0.007) was longer in the MetS group.

Overall LOS was also longer in the MetS group (10 (6) days vs. 10 (5) days, p=0.002) (**Figure 1 A/B/C**). However, in-hospital mortality did not differ between the two groups (1.8% vs. 2.1%, p=0.65)

Transcatheter aortic valve replacement cohort

Baseline patients' characteristic and post-operative results for the TAVR cohort are given in **Supplementary Table 3.** Patients in the MetS group (n=180) had greater burdens of comorbidities than the no-MetS group (n=1948).

Notably, there were no differences in terms of RBC transfused and incidence of post-operative renal failure. Mortality rate did not differ between MetS and no-MetS group (2.8% vs. 3%, p=0.99). Only overall LOS was significantly longer in the MetS group (9 (6) days vs. 8 (6) days, p<0.001) (**Figure 1 A/B/C**).

-Predictors for in-hospital mortality

Age (p<0.001), renal failure (p<0.001), redo surgery (p<0.001), COPD (p=0.002), female sex(p=0.006), and MetS (p=0.003) were independent predictors for in-hospital mortality (full ORs reported in **Supplementary Table 4**). There was a statistically significant interaction between SAVR, TAVR and MetS (p for interaction= 0.004 and 0.003) suggesting lower association to mortality in these cohorts compared to the MVS cohort (reference level). Notably, sensitivity analysis showed BMI (continuous variable) as inversely associated to mortality (p=0.02), while no significant association with mortality, insulin resistance, atherogenic dyslipidaemia and systemic hypertension (**Supplementary Table 5)** .

-Predictors for post-operative LOS

Age (p<0.001), renal failure (p<0.001), COPD (p<0.001), redo surgery (p<0.001), AF (p<0.001), female sex (p<0.001), operation type (Mitral) (p<0.001), and MetS (p=0.02), were independent predictors associated with in-hospital LOS (full coefficients reported in **Supplementary Table 6**).

Sensitivity analysis showed hypertensions (p=0.01) and insulin resistance (p=0.01) as predictors independently associated to post-operative LOS (**Supplementary Table 7**).

In hospital survival probability

For both strata (overall no-MetS and MetS), prolonged hospital stay was associated to increased likelihood for mortality.

In hospital survival at 30, 60, 90 and 120 days was 91% vs. 90%, 64% vs. 67%, 48% vs. 60% and 31% vs. 48%, (no-MetS vs. MetS respectively, p=0.8, log-rank) (**Figure 2 /Supplementary Table 8**).

In between centres mortality variability

Figure 3 depicts the overall in between centres variability and pooled mortality proportion for MetS (4%, (95% CI: 2%, 6%)) and no-MetS (2%, (95% CI: 1%, 3%)). Moderate heterogeneity was observed in the MetS group, however, studies with higher weight (n=3, 5, 7) showed similar magnitude and direction of the effect size.

DISCUSSION

The main findings of study can be summarized as follow:

a) Individuals with MetS, according to the WHO definition, had significant greater burdens of clinical comorbidities;

b) post-operative complications, including prolonged post-operative LOS, were more frequent in the surgical strata MetS group; mortality rate was significant higher in the MVS MetS group;

c) however, in the TAVR cohort, post-operative complications and mortality rate did not differ between patients with and without MetS; overall LOS was longer in the MetS group.

MetS may cause a number of effects on the myocardium and the circulatory system, including myocardial fibrosis, activation on inflammatory and proatherogenic pathways (macrophage infiltration and cytokine gene expression), endothelial dysfunction and heart failure with either preserved or reduced ejection function(13).

To the best of our knowledge, this is the first study that specifically investigated the effect of MetS on post-operative complications after isolated valve intervention.

It is important to notice that MetS in our study was a significant independent predictor for post-operative mortality, however this was largely driven by the mitral cohort. Notably, when controlling for other confounders, systemic hypertension, atherogenic dyslipidaemia and insulin resistance were not significantly associated to mortality. On the contrary, BMI was inversely correlated with mortality. This latter concept is known as 'obesity paradox' and has been described already by others(13, 14).

Nevertheless, there are two important considerations to be made for 'obesity': the first is that not always obesity is synonymous of MetS since there are so-called metabolically healthy obese (MHO) individuals

with high level of insulin sensitivity without systemic hypertension and atherogenic dyslipidaemia and other features of MetS(12, 15). A survey analysis, suggested that MHO may account for a significant percentage of obese population(15). The second consideration is that waist circumference rather than BMI is a more sensitive index for the definition of obesity(16). An epidemiological study showed that, when BMI and waist circumference were included in the same regression model, the latter remained a positive predictor of risk of death while the former was unrelated or inversely related to the risk of death(17). Waist circumference is a more precise index for visceral adiposity / central obesity(16). Visceral obesity causes a decrease in insulin-mediated glucose uptake, insulin resistance and ultimately endothelial dysfunction (3, 5). Nonetheless, waist circumference is seldom measured in the cardiac surgery context, and most studies that investigated the obesity paradox have considered the BMI as measure of obesity, rather than waist circumference(14).

In our study cohort, individuals with MetS had significant greater burdens of comorbidities that included COPD, peripheral vascular and previously treated coronary disease, advanced age, reduced LVEF, renal failure and prevalent female sex. The latter is a proven 'condition of risk' associated to worst outcome in cardiac surgery(18). The association of MetS with those comorbidities can explain the excess mortality and complication rate in this group.

Post-operative LOS was significantly prolonged in the MetS group. The presence of MetS was also independent predictor for increased LOS; also, sensitivity analysis showed diabetes, systemic hypertension but not BMI nor obesity (defined as BMI>30kg/m^2) to be independently associated to LOS.

Evaluating the feasibility and performance of the minimally invasive surgical approach (both mitral and aortic) in individual with MetS is beyond the scope of this research. However, there was no difference in terms of number of patients approached with minimally invasive techniques (mitral and aortic) among MetS and no-MetS.

With the advent of TAVR, many high-risk patients with symptomatic aortic valve stenosis have been treated worldwide. Some studies investigated the effect of specific risk factors (i.e., diabetes / obesity)(19) in patients undergoing TAVR, but none focused on MetS. Two studies found BMI as inversely associated to mortality, while visceral adiposity as independent risk factor for post-operative mortality(20, 21). Those findings confirm the suboptimal accuracy of BMI as trait for MetS. Opposite to the surgical group, in our series we found that MetS was not associated with worst post-operative outcomes in the TAVR subgroup.

Limitation

Beside the known limitations inherent to the retrospective nature of this study we acknowledge some other limitations. For this study, we used the WHO definition for MetS, and perhaps the use of different definitions such as the NCEP/ATP 3 or IDF could have potentially led to different results. For the obesity, the latter two definitions refer more specifically to waist circumferences rather than BMI>30 kg\m^2, pointing the focus to the visceral adiposity(16). Microalbuminuria, an adjunctive criterion for the WHO definition of MetS, was not recoded in our dataset.

Long term follow-up was not carried out; hence we could not evaluate the impact of MetS at distance. In fact, an important aspect of MetS is the tendency to accelerated development of pressure gradient in the bioprosthetic valve(22). Nevertheless, the progression of aortic bioprosthetic valve gradient and stenosis was not investigated.

Conclusions

In this multicentric study, individuals affected by MetS when compared with no-MetS undergoing heart valve surgery experienced more post-operative complications, including prolonged post-operative LOS, with mortality rate significant higher in the MVS group.

In the TAVR cohort, post-operative complications and mortality rate did not differ between patients with and without MetS, however overall LOS was longer in the MetS group.

This data supports the need for further investigation for both risk definition and reduction in patients with MetS, particularly in the context of surgical heart valve surgical intervention.

Figure legends

Figure 1. Post-operative length of stay (LOS), mitral valve surgery (MVS), surgical aortic valve (SAVR) and transcatheter aortic valve replacement (TAVR) cohort, of patients with and without metabolic syndrome (MetS). **A)** Density plot: depicts the distribution (y-axis, %) of LOS (x-axis, days) in the MetS and no-MetS groups**(B)** Jitter-plot: depicts distribution of single LOS values (days) in the MetS vs. no-MetS, **(C)** Box-plot with outliers' visualization.

Figure 2. Kaplan-Meier: In hospital survival at 30, 60, 90 and 120 days: 91% (95% CI: 89%-93%) vs. 90% (95% CI: 85%-94%), 64% (95% CI: 58%-70%) vs. 67% (95% CI: 53%-84%), 48% (95% CI: 40%-58%) vs. 60% (95% CI: 43%-83%) and 31% (95% CI: 20%-47%) vs. 48% (95% CI: 27%-82%), no-MetS vs. MetS respectively, p=0.8 (log-rank)

Table 1. Baseline patients' characteristics and peri-operative outcomes, MVS

	Overall N=6815	No-MetS N=6506	MetS N=309	p
Age, y/o, (mean (SD))	65.5 (12.6)	65.2 (12.7)	70.8 (8.3)	<0.001
BMI kg/m^2 (mean (SD))	25.8 (4.5)	25.5 (4.1)	29.4 (5.9)	<0.001
BMI [?] 30 kg/m^2	664 (9.7)	546 (8.4)	118 (38.2)	<0.001
Sex male, n (%)	3445 (50.6)	3312 (50.9)	133 (43)	0.008
Diabetes, n (%)				<0.001
IDDM, n (%)	85 (1.2)	28 (0.4)	57 (18.4)	
NIDDM, n (%)	325 (4.8)	140 (2.2)	185 (59.9)	
IGT/IFT, n (%)	115 (1.7)	48 (0.7)	67 (21.7)	
Atherogenic dyslipidemia, n (%)	2055 (30.2)	1773 (27.3)	282 (91.3)	<0.001
Systemic hypertension, n (%)	3454 (50.7)	3152 (48.4)	302 (97.7)	<0.001
Creatinine > 1.2 mg/dl	162 (2.4)	134 (2.1)	28 (9.1)	<0.001
COPD, n (%)	319 (4.7)	281 (4.3)	38 (12.3)	<0.001
LVEF, %, (mean (SD))	54 (8.7)	54.2 (8.6)	50.5 (9.5)	<0.001
Peripheral vascular disease, n (%)	136 (2)	113 (1.7)	23 (7.4)	<0.001
Previous CABG/PCI	401 (5.8)	369 (5.6)	32 (10.3)	0.002
Current/ ex-smokers, n (%)	1491 (21.8)	1387 (21.3)	104 (33.6)	<0.001
Redo surgery, n (%)	524 (7.7)	483 (7.4)	41 (13.3)	<0.001
AF[§], n (%)	1628 (23.9)	1505 (23.1)	123 (39.8)	<0.001
Operation type				
Mitral valve repair, n (%)	4560 (66.9)	4361 (67)	199 (64.4)	0.70

Mitral valve replacement, n (%)	2255 (33)	2150 (33)	105 (33.9)	0.85
Associated tricuspid repair, n (%)	1102 (16.1)	1054 (16.2)	48 (15.5)	0.85
Minimally invasive, n (%)	3346 (49.1)	3183 (48.9)	163 (52.8)	0.20
CPB time, min, median (IQR)	87 (46)	81 (43.5)	88 (46)	<0.001
Cross clamp time, min, median (IQR)	66 (41)	59 (43)	62 (30)	0.73
Ventilation time, hours, median (IQR)	7 (5)	7 (6)	8 (7)	0.02
RBC transfused, n (%)[?]	1885 (27.7)	1753 (26.9)	132 (42.7)	<0.001
Invalidating stroke, n (%)	24 (0.4)	23 (0.4)	1 (0.3)	0.99
Renal failure, n (%)	448 (6.6)	386 (5.9)	62 (20.1)	<0.001
ICU LOS, days, median (IQR)	2 (1)	2 (1)	2 (2)	<0.001
Post-operative LOS, days, median (IQR)	10 (6)	10 (6)	11 (9)	<0.001
In-hospital mortality, n (%)	149 (2.2)	129 (2)	20 (6.5)	<0.001

Data are reported as number or frequency or mean and standard deviation (SD) or median and interquartile range (IQR). AF: Atrial fibrillation. BMI: Body mass index. COPD: Chronic obstructive pulmonary disease. CPB: Cardiopulmonary bypass. ICU: Intensive care unit. IDDM: Insulin dependent diabetes mellitus. IGT: Impaired glucose tolerance. IFT: Impaired fasting glucose. LVEF: Left ventricle ejection function. MetS: Metabolic syndrome. MVS: Mitral valve surgery. NIDDM: non-insulin dependent diabetes mellitus. RBC: Red blood cells. [?] Refers to at least 2 units of RBC transfused § Include paroxysmal, persistent and permanent AF.	Data are reported as number or frequency or mean and standard deviation (SD) or median and interquartile range (IQR). AF: Atrial fibrillation. BMI: Body mass index. COPD: Chronic obstructive pulmonary disease. CPB: Cardiopulmonary bypass. ICU: Intensive care unit. IDDM: Insulin dependent diabetes mellitus. IGT: Impaired glucose tolerance. IFT: Impaired fasting glucose. LVEF: Left ventricle ejection function. MetS: Metabolic syndrome. MVS: Mitral valve surgery. NIDDM: non-insulin dependent diabetes mellitus. RBC: Red blood cells. [?] Refers to at least 2 units of RBC transfused § Include paroxysmal, persistent and permanent AF.	Data are reported as number or frequency or mean and standard deviation (SD) or median and interquartile range (IQR). AF: Atrial fibrillation. BMI: Body mass index. COPD: Chronic obstructive pulmonary disease. CPB: Cardiopulmonary bypass. ICU: Intensive care unit. IDDM: Insulin dependent diabetes mellitus. IGT: Impaired glucose tolerance. IFT: Impaired fasting glucose. LVEF: Left ventricle ejection function. MetS: Metabolic syndrome. MVS: Mitral valve surgery. NIDDM: non-insulin dependent diabetes mellitus. RBC: Red blood cells. [?] Refers to at least 2 units of RBC transfused § Include paroxysmal, persistent and permanent AF.	Data are reported as number or frequency or mean and standard deviation (SD) or median and interquartile range (IQR). AF: Atrial fibrillation. BMI: Body mass index. COPD: Chronic obstructive pulmonary disease. CPB: Cardiopulmonary bypass. ICU: Intensive care unit. IDDM: Insulin dependent diabetes mellitus. IGT: Impaired glucose tolerance. IFT: Impaired fasting glucose. LVEF: Left ventricle ejection function. MetS: Metabolic syndrome. MVS: Mitral valve surgery. NIDDM: non-insulin dependent diabetes mellitus. RBC: Red blood cells. [?] Refers to at least 2 units of RBC transfused § Include paroxysmal, persistent and permanent AF.	Data are reported as number or frequency or mean and standard deviation (SD) or median and interquartile range (IQR). AF: Atrial fibrillation. BMI: Body mass index. COPD: Chronic obstructive pulmonary disease. CPB: Cardiopulmonary bypass. ICU: Intensive care unit. IDDM: Insulin dependent diabetes mellitus. IGT: Impaired glucose tolerance. IFT: Impaired fasting glucose. LVEF: Left ventricle ejection function. MetS: Metabolic syndrome. MVS: Mitral valve surgery. NIDDM: non-insulin dependent diabetes mellitus. RBC: Red blood cells. [?] Refers to at least 2 units of RBC transfused § Include paroxysmal, persistent and permanent AF.

Table 2. Baseline patients' characteristics and peri-operative outcomes, SAVR cohort

	Overall N=8340	No-MetS N=7453	Mets N=887	p
Age, y/o, (mean (SD))	71.2 (11.6)	71 (12)	73.5 (7.6)	<0.001

BMI kg/m^2 (mean (SD))	27.4 (4.5)	27 (4.3)	30.2 (5.1)	<0.001
BMI [?] 30 kg/m^2	1391 (16.7)	1015 (13.6)	376 (42.4)	<0.001
Sex male, n (%)	4516 (54.1)	4088 (54.9)	428 (48.3)	<0.001
Diabetes, n (%)				<0.001
IDDM, n (%)	249 (3)	71 (1)	178 (20.1)	
NIDDM, n (%)	780 (9.4)	228 (3.1)	552 (62.2)	
IGT/IFT, n (%)	243 (2.9)	86 (1.2)	157 (17.7)	
Atherogenic dyslipidemia, n (%)	3419 (41)	2616 (35.1)	803 (90.5)	<0.001
Systemic hypertension, n (%)	5085 (61)	4215 (56.6)	870 (98.1)	<0.001
Creatinine > 1.2 mg/dl	253 (3)	196 (2.6)	57 (6.4)	<0.001
COPD, n (%)	537 (6.4)	444 (6)	93 (10.5)	<0.001
LVEF, %, (mean (SD))	55 (8.2)	55 (8.2)	54.8 (7.9)	0.48
Peripheral vascular disease, n (%)	508 (6.1)	404 (5.4)	104 (11.7)	<0.001
Previous CABG/PCI	520 (6.2)	419 (5.6)	101 (11.3)	<0.001
Current/ ex-smokers, n (%)	2203 (26.4)	1861 (24.9)	342 (38.5)	<0.001
Redo surgery, n (%)	533 (6.4)	465 (6.2)	68 (7.7)	0.11
AF[§], n (%)	696 (8.3)	587 (7.9)	109 (12.3)	<0.001
Minimally invasive, n (%)	4205 (50.4)	4270 (51.1)	724 (47.2)	0.20
CPB time, min, median (IQR)	76 (34)	75 (35)	79 (33)	0.005
Cross clamp time, min, median (IQR)	60 (29)	60 (28)	62 (27)	0.007
Ventilation time, hours, median (IQR)	7 (5)	7 (6)	7 (5)	0.26
RBC transfused, n (%)[?]	2424 (29.1)	2067 (27.7)	357 (40.2)	<0.001
Invalidating stroke, n (%)	34 (0.4)	29 (0.4)	5 (0.6)	0.99
Renal failure, n (%)	509 (616)	419 (5.6)	90 (10.1)	<0.001
ICU LOS, days, median (IQR)	2 (1)	2 (1)	2 (2)	0.007
Post-operative LOS, days, median (IQR)	10 (6)	10 (5)	10 (6)	0.002

In-hospital mortality, n (%)	172 (2.1)	156 (2.1)	16 (1.8)	0.65
Data are reported as number or frequency or mean and standard deviation (SD) or median and interquartile range (IQR). AF: Atrial fibrillation. BMI: Body mass index. COPD: Chronic obstructive pulmonary disease. CPB: Cardiopulmonary bypass. ICU: Intensive care unit. IDDM: Insulin dependent diabetes mellitus. IGT: Impaired glucose tolerance. IFT: Impaired fasting glucose. LVEF: Left ventricle ejection function. MetS: Metabolic syndrome. NIDDM: non-insulin dependent diabetes mellitus. RBC: Red blood cells. SAVR: Surgical aortic valve replacement. [?] Refers to at least 2 units of RBC transfused § Include paroxysmal, persistent and permanent AF.	Data are reported as number or frequency or mean and standard deviation (SD) or median and interquartile range (IQR). AF: Atrial fibrillation. BMI: Body mass index. COPD: Chronic obstructive pulmonary disease. CPB: Cardiopulmonary bypass. ICU: Intensive care unit. IDDM: Insulin dependent diabetes mellitus. IGT: Impaired glucose tolerance. IFT: Impaired fasting glucose. LVEF: Left ventricle ejection function. MetS: Metabolic syndrome. NIDDM: non-insulin dependent diabetes mellitus. RBC: Red blood cells. SAVR: Surgical aortic valve replacement. [?] Refers to at least 2 units of RBC transfused § Include paroxysmal, persistent and permanent AF.	Data are reported as number or frequency or mean and standard deviation (SD) or median and interquartile range (IQR). AF: Atrial fibrillation. BMI: Body mass index. COPD: Chronic obstructive pulmonary disease. CPB: Cardiopulmonary bypass. ICU: Intensive care unit. IDDM: Insulin dependent diabetes mellitus. IGT: Impaired glucose tolerance. IFT: Impaired fasting glucose. LVEF: Left ventricle ejection function. MetS: Metabolic syndrome. NIDDM: non-insulin dependent diabetes mellitus. RBC: Red blood cells. SAVR: Surgical aortic valve replacement. [?] Refers to at least 2 units of RBC transfused § Include paroxysmal, persistent and permanent AF.	Data are reported as number or frequency or mean and standard deviation (SD) or median and interquartile range (IQR). AF: Atrial fibrillation. BMI: Body mass index. COPD: Chronic obstructive pulmonary disease. CPB: Cardiopulmonary bypass. ICU: Intensive care unit. IDDM: Insulin dependent diabetes mellitus. IGT: Impaired glucose tolerance. IFT: Impaired fasting glucose. LVEF: Left ventricle ejection function. MetS: Metabolic syndrome. NIDDM: non-insulin dependent diabetes mellitus. RBC: Red blood cells. SAVR: Surgical aortic valve replacement. [?] Refers to at least 2 units of RBC transfused § Include paroxysmal, persistent and permanent AF.	Data are reported as number or frequency or mean and standard deviation (SD) or median and interquartile range (IQR). AF: Atrial fibrillation. BMI: Body mass index. COPD: Chronic obstructive pulmonary disease. CPB: Cardiopulmonary bypass. ICU: Intensive care unit. IDDM: Insulin dependent diabetes mellitus. IGT: Impaired glucose tolerance. IFT: Impaired fasting glucose. LVEF: Left ventricle ejection function. MetS: Metabolic syndrome. NIDDM: non-insulin dependent diabetes mellitus. RBC: Red blood cells. SAVR: Surgical aortic valve replacement. [?] Refers to at least 2 units of RBC transfused § Include paroxysmal, persistent and permanent AF.

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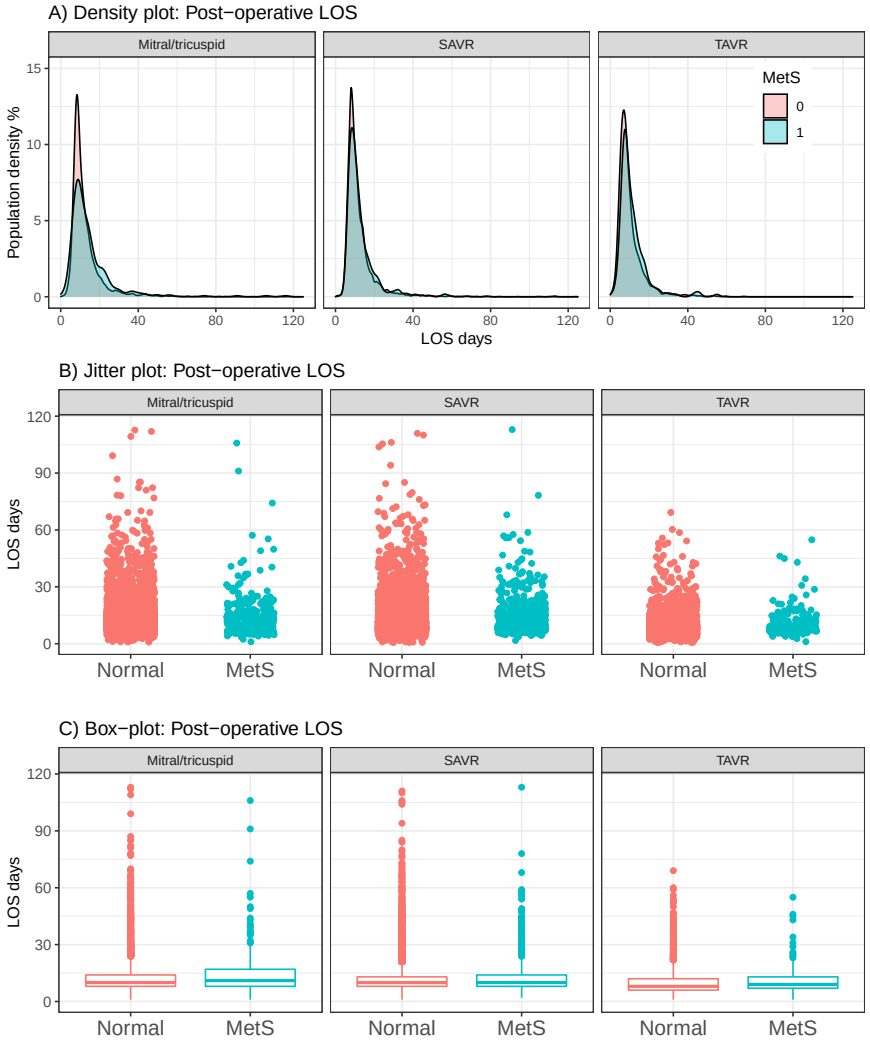

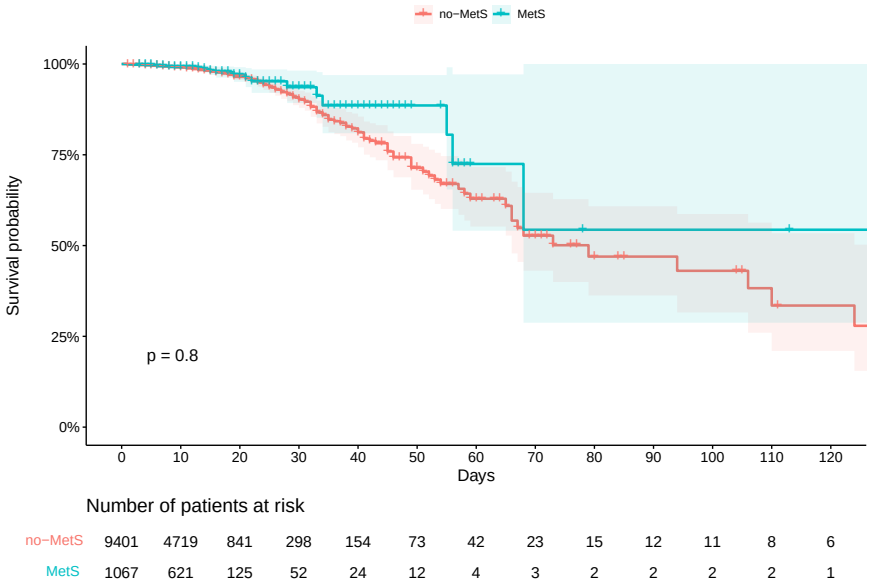

Study or Subgroup	Events	Total	Weight	IV, Random, 95% CI
Group = MetS				
1	2	162.0	2.7%	0.01 [0.00; 0.05]
2	3	171.0	3.5%	0.02 [0.01; 0.05]
3	5	93.0	4.4%	0.05 [0.02; 0.12]
4	0	38.0	0.9%	0.00 [0.00; 0.17]
5	17	358.0	6.6%	0.05 [0.03; 0.08]
6	3	60.0	3.4%	0.05 [0.02; 0.14]
7	8	79.0	5.3%	0.10 [0.05; 0.19]
8	0	0.5	0.6%	0.00 [0.02; 0.94]
9	1	139.0	1.6%	0.01 [0.00; 0.05]
10	2	96.0	2.7%	0.02 [0.01; 0.08]
Total (95% CI)		**1196.5**	**31.6%**	**0.04 [0.02; 0.06]**
Prediction interval	.	.	−−	**[0.01; 0.15]**
Heterogeneity: Tau^2 = 0.3753; Chi^2 = 19.36, df = 9 (P = 0.02); I^2 = 54%				
Group = noMetS				
1	54	1937.0	7.6%	0.03 [0.02; 0.04]
2	21	1175.0	6.9%	0.02 [0.01; 0.03]
3	30	1605.0	7.2%	0.02 [0.01; 0.03]
4	10	560.0	5.8%	0.02 [0.01; 0.03]
5	95	3718.0	7.9%	0.03 [0.02; 0.03]
6	47	1046.0	7.5%	0.04 [0.03; 0.06]
7	42	1020.0	7.5%	0.04 [0.03; 0.06]
8	5	448.0	4.5%	0.01 [0.00; 0.03]
9	22	1411.0	6.9%	0.02 [0.01; 0.02]
10	17	1039.0	6.6%	0.02 [0.01; 0.03]
Total (95% CI)		**13959.0**	**68.4%**	**0.02 [0.02; 0.03]**
Prediction interval	.	.	−−	**[0.01; 0.06]**
Heterogeneity: Tau^2 = 0.1477; Chi^2 = 44.95, df = 9 (P < 0.01); I^2 = 80%				
Total (95% CI)		**15155.5**	**100.0%**	**0.03 [0.02; 0.03]**
Heterogeneity: Tau^2 = 0.2485; Chi^2 = 75.20, df = 19 (P < 0.01); I^2 = 75%