Peer Review File

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Reviewer A

Comment 1. The background section of the abstract should be implemented by clearly including the aims of the paper. Please revise this section.

Reply 1. We added the following sentence in the abstract section.

Changes in the text:

<Abstract section>

Therefore, the current study was designed to characterize SAS-IMAF in patients receiving CABG with IMA. (see Page 4, line 6-7)

Comment 2. Authors should include the pharmacological background of patients. Drugs might impact on outcomes and occurrence of final endpoints. Please update data and include them in the final regression analysis.

Reply 2.

- We included the use of "DAPT", "β-blocker", "ACE inhibitor or ARB" and "statin" into uni- and multivariate analyses. Even after adjusting these medication use, SAS-IMAF was an independent predictor of MACE (HR=4.04, 95%CI: 1.44-11.38, P=0.008).
- In the revised manuscript, we presented these data in Table 4 and Table S4-6. In addition, we revised sentences about the results of multivariate analysis.

Table 4. Univariate and Multivariate Analysis of Predictors for MACE

	Univariate analysis			Multivariate analysis (Model 1)			Multivariate analysis (Model 2)		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
SAS-IMAF	5.82	2.31-14.65	<0.001	5.34	2.10-13.57	<0.001	4.04	1.44-11.38	0.008
Age ≧75 years	1.60	0.88-2.92	0.12	1.57	0.85-2.90	0.15	1.20	0.59-2.43	0.61
Female	0.57	0.22-1.50	0.25	0.60	0.23-1.62	0.32	0.78	0.26-2.34	0.66
Hypertension	1.38	0.52-3.68	0.51	-	-	-	-	-	-
Dyslipidemia	0.72	0.35-1.50	0.39	-	-	-	-	-	-
Type 2 DM	1.16	0.63-2.13	0.64	-	-	-	-	-	-
CKD	2.26	1.16-4.41	0.02	-	-	-	1.77	0.83-3.80	0.14
Previous MI	1.70	0.94-3.10	0.08	-	-	-	1.20	0.57-2.54	0.62
Previous stroke	1.31	0.66-2.59	0.45	-	-	-	-	-	-
LVEF <40%	2.69	1.42-5.10	0.002	-	-	-	2.40	1.09-5.25	0.03

Table S4. Univariate and Multivariate Analysis of Predictors for Cardiac Death

	Univariate analysis			Multivariate analysis (Model 1)			Multivariate analysis (Model 2)		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
SAS-IMAF	3.14	0.98-10.05	0.05	2.88	0.89-9.31	0.08	1.75	0.45-6.80	0.42
Age ≧75 years	1.50	0.70-3.22	0.29	1.48	0.69-3.20	0.31	1.20	0.49-2.91	0.69
Female	0.60	0.18-2.08	0.43	0.63	0.18-2.16	0.46	0.70	0.17-2.86	0.62
Hypertension	2.09	0.48-9.07	0.33	-	-	-	-	-	-
Dyslipidemia	0.44	0.19-1.01	0.05	-	-	-	0.56	0.19-1.71	0.31
Type 2 DM	1.60	0.71-3.62	0.26	-	-	-	-	-	-
CKD	3.75	1.40-10.06	0.009	-	-	-	2.93	1.01-8.54	0.05
Previous MI	2.25	1.05-4.84	0.04	-	-	-	1.33	0.53-3.33	0.54
Previous stroke	1.15	0.47-2.80	0.76	-	-	-	-	-	-
LVEF <40%	5.57	2.52-12.33	<0.001	-	-	-	4.13	1.63-10.49	0.003
ACS	4.46	1.92-10.36	<0.001	-	-	-	4.56	1.75-11.91	0.002

Table S5. Univariate and Multivariate Analysis of Predictors for Non-fatal MI

	Univariate analysis			Multivariate analysis (Model 1)			Multivariate analysis (Model 2)		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
SAS-IMAF	7.45	1.36-40.94	0.02	8.65	1.46-51.26	0.02	4.37	0.63-30.18	0.13
Age ≧75 years	1.59	0.35-7.21	0.55	1.32	0.28-6.18	0.73	1.21	0.24-6.16	0.82
Female	2.22	0.42-11.71	0.35	2.81	0.49-16.15	0.25	4.65	0.71-30.32	0.11
Hypertension	-	-	-	-	-	-	-	-	-
Dyslipidemia	0.53	0.10-2.78	0.45	-	-	-	-	-	-
Type 2 DM	1.76	0.34-9.18	0.50	-	-	-	-	-	-
CKD	4.41	0.53-37.00	0.17	-	-	-	-	-	-
Previous MI	0.68	0.13-3.56	0.65	-	-	-	-	-	-
Previous stroke	0.59	0.07-4.98	0.63	-	-	-	-	-	-
LVEF <40%	1.42	0.27-7.44	0.68	-	-	-	-	-	-
ACS	3.89	0.74-20.30	0.11	-	-	-	3.94	0.62-24.80	0.14

Table S6. Univariate and Multivariate Analysis of Predictors for Non-fatal Ischemic Stroke

	Univariate analysis			Multivariate analysis (Model 1)			Multivariate analysis (Model 2)		
	HR	95% CI	P value	HR	95% CI	P value	HR	95%CI	P value
SAS-IMAF	6.68	2.17-20.52	<0.001	6.03	1.93-18.80	0.002	7.72	2.33-25.58	<0.001
Age ≧75 years	1.99	0.80-4.92	0.14	1.91	0.76-4.81	0.17	1.80	0.65-4.97	0.26
Female	0.56	0.13-2.45	0.44	0.61	0.13-2.74	0.51	0.78	0.17-3.67	0.76
Hypertension	0.88	0.25-3.12	0.85	-	-	-	-	-	-
Dyslipidemia	2.11	0.48-9.27	0.32	-	-	-	-	-	-
Type 2 DM	1.15	0.46-2.83	0.77	-	-	-	-	-	-
CKD	1.46	0.57-3.70	0.43	-	-	-	-	-	-
Previous MI	1.59	0.66-3.86	0.30	-	-	-	-	-	-
Previous stroke	1.46	0.55-3.89	0.45	-	-	-	-	-	-
LVEF <40%	0.60	0.17-2.11	0.43	-	-	-	-	-	-
ACS	1.71	0.71-4.14	0.23	-	-	-	-	-	-

Changes in the text:

<Abstract section>

Multivariate Cox proportional hazards model (hazard ratio (HR)=4.04, 95%CI: 1.44-11.38, P=0.008) and propensity score-matched analyses (HR=2.67, 95%CI: 1.06-6.73, P=0.038) consistently demonstrated the association of SAS-IMAF with MACE. (see Page 5, line 3-4)

<Results section>

- Even after adjusting for age and gender (Model 1), and other covariates including medication use (DAPT, β-blocker, ACE inhibitor or ARB, and statin) (Model 2), SAS-IMAF was still an independent predictor of MACE (Model 1: HR=5.34, 95%CI: 2.10-13.57, P<0.001, Model 2: HR=4.04, 95%CI: 1.44-11.38, P=0.008, Table 4). (see Page 14, line 8-11)

- On multivariate analysis, SAS-IMAF still continued to predict the occurrence of non-fatal ischemic stroke (HR=7.72, 95%CI: 2.33-25.58, P<0.001, Table S6). (see Page 14, line 15-16)

Comment 3. It is hard to understand if patients were on target for their recommended values in term of lipid concentrations, blood pressure control, etc. This should be clearly stated, discussed, and included in the analysis as it might impact on results. Please provide.

Reply 3.

- In the current study, we were able to collect on-treatment LDL-C and blood pressure levels in 84.2% of study subjects (=320/380). Of these, on-treatment LDL-C <70 mg/dL

was achieved in 49.7 % of them. The frequency of patients who achieved both SBP<140 mmHg and DBP <90 mmHg was 83.4%.

- We conducted multivariate analysis in 320 patients who had on-treatment LDL-C and blood pressure data. As shown in the following table, even after adjusting on-treatment LDL-C <70 mg/dL and SBP<140 mmHg + DBP <90 mmHg, SAS-IMAF still independently predicted the occurrence of MACE (HR=5.55, 95%CI: 1.54-20.07, P=0.009).
- In the revised manuscript, we added the following sentences in the Results section. Furthermore, the aforementioned Table was presented as Table S2 and S7, respectively.

Table S2. Comparison of On-treatment LDL-C and BP levels

	Overall (n=320)	SAS-IMAF (+) (n=16)	SAS-IMAF (-) (n=304)	P value
On-treatment LDL-C (mg/dL)	74.2±28.9	69.1±38.9	74.5±28.4	0.47
On-treatment LDL-C <70mg/dL, n (%)	159 (49.7)	11 (68.8)	148 (48.7)	0.12
On-treatment SBP (mmHg)	122±21	112±23	122±21	0.06
On-treatment DBP (mmHg)	63±13	57±10	63±13	0.05
On-treatment SBP <140mmHg and DBP <90mmHg, n (%)	267 (83.4)	15 (93.8)	252 (82.9)	0.25

BP=blood pressure, DBP=diastolic blood pressure, LDL-C= low-density lipoprotein-cholesterol, SAS-IMAF=subclavian artery stenosis related internal mammary artery failure, SBP=systolic blood pressure

Table S7. Univariate and Multivariate Analysis of Predictors for MACE in Patients with On-treatment LDL-C and BP Levels

	Univariate analysis			Multivariate analysis (Model 1)			Multivariate analysis (Model 2)		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
SAS-IMAF	10.69	3.71-30.84	<0.001	9.09	3.09-26.76	<0.001	5.55	1.54-20.07	0.009
Age ≧75 years	2.30	1.11-4.78	0.03	1.99	0.93-4.28	0.08	1.54	0.62-3.83	0.35
Female	0.70	0.23-2.07	0.51	0.75	0.24-2.33	0.62	0.98	0.26-3.64	0.97
Hypertension	1.18	0.40-3.55	0.76	-	-	-	-	-	-
Dyslipidemia	1.08	0.40-2.95	0.88	-	-	-	-	-	-
Type 2 DM	0.99	0.48-2.04	0.98	-	-	-	-	-	-
CKD	3.31	1.39-7.84	0.007	-	-	-	2.23	0.84-5.92	0.11
Previous MI	1.60	0.78-3.28	0.20	-	-	-	-	-	-
Previous stroke	1.67	0.76-3.70	0.20	-	-	-	-	-	-
LVEF <40%	2.42	1.12-5.23	0.02	-	-	-	2.12	0.83-5.41	0.12
ACS	4.2	1.93-9.13	<0.001	-	-	-	6.46	2.35-17.78	<0.001

Changes in the text:

<Results section>

- *In the current study, on-treatment low-density lipoprotein-cholesterol (LDL-C), systolic blood pressure and diastolic blood pressure levels were obtained in 84.2% (=320/380) of study subjects. These risk controls did not differ between those with and without SAS-IMAF (Table S2). (see Page 13, line 16-18~ Page 14, line 1-2)*
- *In 320 patients with on-treatment LDL-C, systolic blood pressure and diastolic blood pressure levels, multivariate analyses adjusting this risk controls consistently demonstrated the association of SAS-IMAF with the occurrence of MACE (HR=5.55, 95%CI: 1.54-20.07, P=0.009, Table S7). (see Page 14, line 16-19)*

Comment 4. What about timing of surgery, duration of intervention, type of treatment? Please discuss.

Reply 4.

- We summarized the detailed timing of initial and additional revascularization procedures in SAS-IMAF patients. The timing of revascularization procedures and its selection vary in each individual. Future studies are warranted to standardize selection and timing of therapeutic approach in patients with SAS-IMAF.
- In the revised manuscript, we added the following sentences in the Results and Discussion section. In addition, the aforementioned Table was presented as Table S1.

Table S1. Time Course of Revascularization in Patients with SAS-IMAF

ACS (n=15)	
Initial revascularization	Duration from admission to the procedure, days
PCI (n=9)	2.7 ± 2.7
EVT (n=5)	11.8 ± 11.1
Bypass surgery (n=1)	1
Additional Revascularization	Duration from the initial procedure to additional one, days
EVT (n=6)	11.5 ± 9.0
Bypass surgery (n=1)	42
SIHD (n=6)	
Initial revascularization	Duration from admission to the procedure, days
PCI only (n=1)	1
EVT only (n=5)	28.2 ± 21.2

ACS=acute coronary syndrome, EVT=endovascular treatment, PCI=percutaneous coronary intervention, SAS-IMAF=subclavian artery stenosis related internal mammary artery failure, SIHD=stable ischemic heart disease

Changes in the text:

<Results section>

The detailed timing of initial and additional revascularization procedures in patients with SAS-IMAF was summarized in Table S1. (see Page 13, line 11-12)

<Discussion section>

- Table S1 presents the detailed timing of initial and additional revascularization procedures in patients with SAS-IMAF. The timing of revascularization procedures and its selection varied in each individual. Future studies are warranted to standardize selection and timing of therapeutic approach in patients with SAS-IMAF. (see Page 17, line 19~Page 18, line 1-4)

- These observations suggest difficulties to evaluate subclavian artery and have mutual discussion between interventionalist and surgeons in the setting of ACS. (see Page 18, line 9-11)

Comment 5. The retrospective nature of this paper is a limitation of this paper. This should be discussed in a dedicated limitation section. Please provide.

Reply 5. We added the following sentence in the Limitation section.

Changes in the text:
<Study Limitations section>
Firstly, this was a retrospective observational study, but not prospective randomized one. Therefore, management of SAS-IMAF was not standardized but selected according to each physician's discretion. This may be a potential bias. (see Page 19, line 15-18)

Comment 6. Doppler ultrasound evaluation is often forgotten from clinicians when preparing patients to CABG. Please discuss such a point also in relation to the potential skill of Doppler ultrasound for the follow-up of patients and LIMA after CABG. Authors might also consider the paper from Scicchitano P et al. Biomedicines. 2022 Dec 27;11(1):66.
Reply 6. We added the following sentences in the Discussion section. The following paper was cited as reference (29).

Changes in the text:
<Discussion section>
Doppler ultrasound is a non-invasive approach to evaluate subclavian artery stenosis. However, in the real-world clinical practice, all of patients who has received CABG using IMA do not necessarily receive Doppler ultrasound for follow-up evaluation of subclavian artery. The another issue of Doppler ultrasound is inter- and intra-observer variabilities (29). It is required to improve awareness of physicians toward the importance of Doppler ultrasound for evaluation of subclavian artery in patients who have received CABG. More standardized evaluation of subclavian artery with Doppler ultrasound is clinically needed as well. (see Page 18, line 19~Page 19, line 1-6)

<References section>
29. Scicchitano P, De Palo M, Parisi G, Gioia MI, Ciccone MM. Doppler Ultrasound Selection and Follow-Up of the Internal Mammary Artery as Coronary Graft. Biomedicines. 2022;11(1). (see Page 25, line 11-12)

Reviewer B

Comment 1. The main objective of the paper is to compare the clinical characteristics and outcomes of patients with and without SAS-IMAF. The statistical analysis is well performed. However regarding the propensity matching analysis the authors should share the preoperative variables chosen for PSM.

Reply 1. We stated the selected variables for PSM in the Statistical analysis section as follows.

Changes in the text:

<Statistical analysis section>

To conduct propensity score matching (PSM) analysis for balancing the baseline characteristics of patients with and without SAS-IMAF, we obtained propensity score by using multivariable logistic regression models, with the depending variable of SAS-IMAF and following covariates: age, gender, kidney function, left ventricular ejection fraction (LVEF), ACS and the use of statin. (see Page 11, line 3-8)

Comment 2. In addition, the PSM analysis selected 21 and 63 patients. So, I assume that the PSM has been set to a 1:3 ratio. These details should also be discussed.

Reply 2. The reviewer is correct. 1:3 matching was fixed rate matching which was reported not recommended to use due to leading increase in bias. Therefore, we changed the analysis method to variable-rate matching (one-to-many matching), which is reported removing more bias than one-to-one matching and particularly useful when the number of control group is much larger than the number of case group. We added the following sentences in the Statistical analysis section, and the following three papers in the Reference section. In addition, we revised sentences about the results of PSM analysis as follows and presented clinical characteristics data of PSM subjects in Table S8.

Table S8. Clinical Characteristics of Propensity Score-matched Subjects

	SAS-IMAF (+) (n=21)	SAS-IMAF (-) (n=53)	P value	Standardized mean difference
MACE, n (%)	9 (42.9)	9 (17.0)	0.041	0.59
MACE (days)	953 ± 784	950 ± 685	0.99	0.003
Age (years)	74.4±6.7	76.1±7.9	0.30	0.23
Age ≧ 75 years, n (%)	12 (57.1)	32 (60.4)	1	0.07
Female, n (%)	1 (4.8)	2 (3.8)	1	0.05
Hypertension, n (%)	20 (95.2)	42 (79.2)	0.18	0.49
Dyslipidemia, n (%)	16 (76.2)	39 (73.6)	1	0.06
Type 2 DM, n (%)	13 (61.9)	31 (58.5)	0.99	0.07
Smoking, n (%)	5 (23.8)	4 (7.5)	0.13	0.46
CKD, n (%)	16 (76.2)	38 (71.7)	0.92	0.10
Previous MI, n (%)	9 (42.9)	23 (43.4)	1	0.01
Previous stroke, n (%)	11 (52.4)	15 (28.3)	0.09	0.51
LVEF (%)	42.8 ± 15.3	44.4 ± 14.4	0.68	0.10
LVEF <40%, n (%)	8 (38.1)	20 (37.7)	1	0.007
ACS, n (%)	15 (71.4)	36 (67.9)	0.99	0.08

Changes in the text:

<Abstract section>

Multivariate Cox proportional hazards model (hazard ratio (HR)=4.04, 95%CI: 1.44-11.38, P=0.008) and propensity score-matched analyses (HR=2.67, 95%CI: 1.06-6.73, P=0.038) consistently demonstrated the association of SAS-IMAF with MACE. (see Page 5, line 4-5)

<Statistical analysis section>

The settings of PSM were variable-rate (one-to-many) matching which is reported as well-removing bias method (16-18), and caliper of 0.25 to balance the patients with and without SAS-IMAF. After obtaining the matched group patients with and without SAS-IMAF, we performed Cox regression analysis and obtained HRs with 95% confidence interval (CI). (see Page 11, line 8-12)

<Results section>

This analysis matched 21 and 53 patients with and without SAS-IMAF, respectively, and were well matched (Table S8). Even in this PSM cohort, SAS-IMAF continued to predict

the occurrence of MACE significantly (HR=2.67, 95%CI: 1.06-6.73, P=0.038, Figure S2). (see Page 15, line 2-5)

<References section>

16. Cepeda MS, Boston R, Farrar JT, Strom BL. Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. Am J Epidemiol. 2003;158(3):280-7.

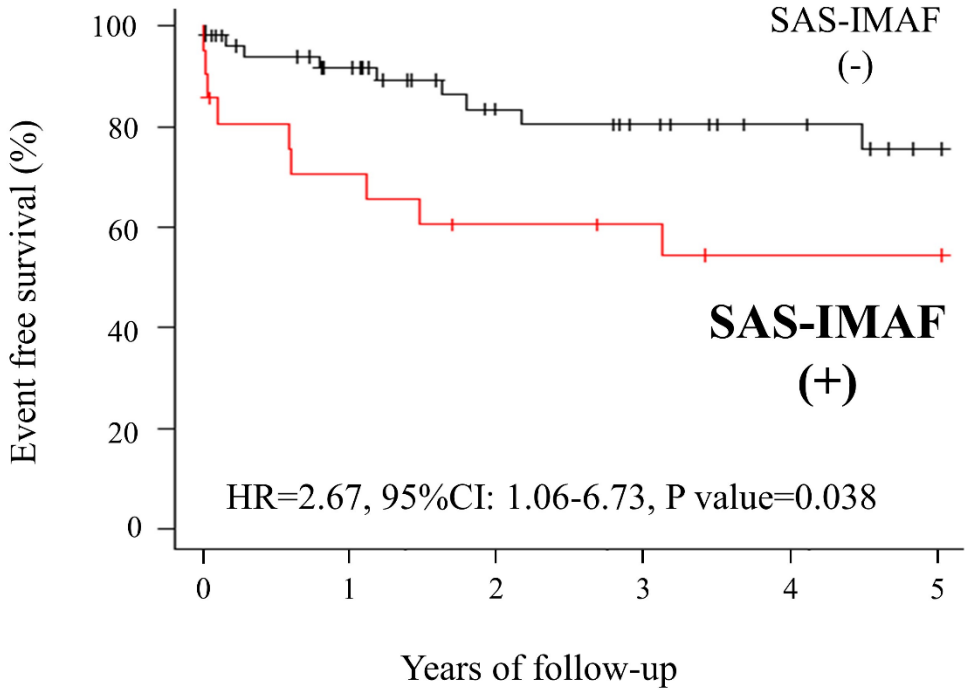
17. Gu XS, Rosenbaum PR. Comparison of Multivariate Matching Methods: Structures, Distances, and Algorithms. Journal of Computational and Graphical Statistics. 1993;2(4):405-20.

18. Ming K, Rosenbaum PR. Substantial gains in bias reduction from matching with a variable number of controls. Biometrics. 2000;56(1):118-24.

(see Page 24, line 7-13)

Comment 3. The PSM analysis is probably the best method to investigate and compare the outcomes between the two groups while mitigating the preoperative differences. For these reasons the authors should present and discuss postoperative results among matched groups.

Reply 3. In the revised manuscript, we presented the following figure about cardiovascular outcomes of matched cohort as Figure S2. Furthermore, we added the following sentence in the Supplementary Figure Legends section.



Changes in the text:

<Supplementary Figure Legends section>

Supplementary Figure 2. The occurrence of MACE in Propensity Score-matched Cohort

The red and black lines indicate the event-free survival curve in patients with and without SAS-IMAF, respectively.

CI=confidence interval, HR=hazard ratio, MACE=major adverse cardiovascular events, SAS-IMAF=subclavian artery stenosis related internal mammary artery failure (see Page 27~28)

Comment 4. As the authors well explained in the discussion section, the difference in clinical outcomes between the two groups is likely multifactorial depending on patients characteristics and procedural details. In this regard, I think the authors should discuss the results of coronary artery revascularization with different surgical approaches (ie sternotomy, MIDCAB, robotic assisted MIDCAB).
Please use these references to discuss and to enrich the discussion section.

CABG :
Gaudino M, Andreotti F, Kimura T. Current concepts in coronary artery revascularisation. Lancet. 2023 May 13;401(10388):1611-1628. doi: 10.1016/S0140-6736(23)00459-2. Epub 2023 Apr 27. PMID: 37121245.

MIDCAB :
Davierwala PM, Verevkin A, Bergien L, von Aspern K, Deo SV, Misfeld M, Holzhey D, Borger MA. Twenty-year outcomes of minimally invasive direct coronary artery bypass surgery: The Leipzig experience. J Thorac Cardiovasc Surg. 2023 Jan;165(1):115-127.e4. doi: 10.1016/j.jtcvs.2020.12.149. Epub 2021 Feb 17. PMID: 33757682.

robotic assisted MIDCAB (RA-MIDCAB) :
Piperata A, Busuttil O, Jansens JL, Modine T, Pernot M, Labrousse L. A Single Center Initial Experience with Robotic-Assisted Minimally Invasive Coronary Artery Bypass Surgery (RA-MIDCAB). J Pers Med. 2022 Nov 12;12(11):1895. doi: 10.3390/jpm12111895. PMID: 36422071; PMCID: PMC9694867.

Reply 4. We added the following sentences in the Discussion section. In addition, the following three papers were added in the Reference section.

Changes in the text:
<Discussion section>
Recently, increasing attentions have focused on minimally invasive approaches of CABG (23). Minimally invasive direct coronary artery bypass (MIDCAB) surgery and its robotic-assisted one have been shown to reduce the length of hospital stay and the surgery-related complication while presenting similar clinical efficacy compared to conventional CABG (24)(25). These more advanced CABG procedures may improve cardiovascular outcomes in patients with SAS-IMAF. Future studies are warranted to

elucidate whether MIDCAB surgery could affect clinical course in patients with and without SAS. (see Page 17, line 6-12)

<References section>

23. Gaudino M, Andreotti F, Kimura T. Current concepts in coronary artery revascularisation. Lancet. 2023;401(10388):1611-28.

24. Davierwala PM, Verevkin A, Bergien L, von Aspern K, Deo SV, Misfeld M, et al. Twenty-year outcomes of minimally invasive direct coronary artery bypass surgery: The Leipzig experience. J Thorac Cardiovasc Surg. 2023;165(1):115-27.e4.

25. Piperata A, Busuttil O, Jansens JL, Modine T, Pernot M, Labrousse L. A Single Center Initial Experience with Robotic-Assisted Minimally Invasive Coronary Artery Bypass Surgery (RA-MIDCAB). J Pers Med. 2022;12(11). (see Page 24, line 26-33)