

Mesenteric Ischemia After Cardiac Surgery in Dialysis Patients: An Overlooked Risk Factor

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ABSTRACT

Background: No study has examined the association of the calcification of abdominal artery orifices with nonocclusive mesenteric ischemia (NOMI) in dialysis patients undergoing cardiac surgery. Thus, this study aimed to determine whether calcification of abdominal blood vessel orifices in hemodialysis patients may be a risk factor for NOMI and examine the long-term survival of dialysis patients after undergoing cardiac surgery.

Methods: From April 2014 to September 2020, 100 dialysis patients underwent cardiac surgery at our hospital. The calcification of the celiac artery (CA) and superior mesenteric artery (SMA) was evaluated by computed tomography, and the degree of orifice stenosis was graded as follows: patent, 0; partial occlusion, 1; and complete occlusion, 2.

Results: Eight patients experienced NOMI, and all of them died. SMA calcification scores were not significantly different between the NOMI and non-NOMI groups (1.38 ± 0.52 vs. 1.13 ± 0.69 ; $P = 0.247$). However, the average CA orifice calcification score was significantly greater in the NOMI group than in the non-NOMI group (1.63 ± 0.52 vs. 1.15 ± 0.65 ; $P = 0.039$), and the SMA+CA orifice calcification scores were significantly different between the groups (3.00 ± 0.76 vs. [non-NOMI] 2.25 ± 1.18 ; $P = 0.028$). In all patients, the 30-day and in-hospital mortality rates were 13% and 18%, respectively. All patients were completely followed up with a mean follow-up period of 604 ± 585 days. Kaplan-Meier survival curves showed that patients with SMA and CA calcification tended to have a shorter overall survival than patients without calcification; however, no significant difference was noted.

Conclusions: The calcification of CA and/or SMA orifices was associated with postoperative NOMI and poor long-term survival among dialysis patients undergoing cardiac surgery.

INTRODUCTION

Nonocclusive mesenteric ischemia (NOMI) is a life-threatening complication after cardiac surgery, with a reported incidence rate between 0.9% and 9.0% [Groesdonk 2013; Klotz 2001]. Additionally, preoperative renal insufficiency requiring hemodialysis is one of the several risk factors for NOMI development after cardiac surgery [Groesdonk 2013; Sakamoto 2020].

Generally, vascular calcification, including aortic calcification, is highly prevalent in hemodialysis patients, and mineral metabolism disorders have been reported as risk factors for vascular calcification [Chertow 2004; Davies 2001; Taniwaki 2005]. Moreover, severe atherosclerosis with calcification at the celiac artery (CA) and the superior mesenteric artery (SMA) was a known risk factor for developing NOMI [Guillaume 2017; Acosta 2006; Juif 2021]. Few studies have focused on the relationship between mesenteric artery calcium and chronic mesenteric ischemia in non-cardiac surgical patients [Terlouw 2021; Terlouw 2021]; however, patients undergoing cardiac surgery would have different risk profiles from those of the general population.

As all hemodialysis patients are not at a high risk of developing NOMI after cardiac surgery, there may be some additional conditions that contribute to the risk of developing NOMI, but those are not yet known. Furthermore, to the best of our knowledge, no studies have examined the association of the calcification of abdominal artery orifices with NOMI in dialysis patients undergoing cardiac surgery. Therefore, this study aimed to determine whether calcification of abdominal blood vessel orifices in hemodialysis patients may be a risk factor for NOMI and to examine the relationship between calcification of abdominal blood vessel orifices and long-term survival in dialysis patients undergoing cardiac surgery.

MATERIALS AND METHODS

The Institutional Review Board of the Asahikawa Medical University Research Ethics Board approved this study (ID: 20108) and waived the need for individual patient consent owing to the retrospective nature of the study.

Patient cohort: This retrospective study enrolled hemodialysis patients who underwent cardiac surgery at our hospital between April 2014 and September 2020. Emergent surgical cases and off-pump cases also were included in our

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review. Additionally, patient medical records retrospectively were analyzed, and long-term follow-up data were obtained from visits at an outpatient clinic and/or through telephone interviews.

Perioperative volume and pharmacological management: During and after the operation, adequate volume management was performed as keeping serum lactate value under 20 mg/dL, and hemodialysis was started on postoperative day 1 using continuous hemodiafiltration. The filtration volume was started as 40 mL/h, and the filtration rate gradually was increased. The systolic blood pressure was kept higher than 100 mmHg, and to maintain the blood pressure, dopamine or norepinephrine was administered. In cases where more than 0.1 µg/kg/min of norepinephrine was needed, vasopressin also was administered.

Diagnosis of NOMI: After cardiac surgery, patients with suspected bowel ischemia due to abdominal distension with an absence of bowel sounds, acute abdominal pain, vomiting, hematochezia, or abnormal laboratory data underwent urgent abdominal contrast-enhanced computed tomography (CT). Disruption of bowel arteries, mesenteric fat stranding, air in the bowel wall, and narrowed superior mesenteric vein were considered signs of NOMI [Mazzei 2015]; however, NOMI finally was diagnosed by either a radiologist who reviewed the CT images followed by autopsy ($N = 3$) or a surgical laparotomy ($N = 5$).

Calcification scoring: Calcification of CA and SMA orifices was evaluated and scored by CT. CT examinations were performed using 5-mm slices in the axial or sagittal planes (Figure 1) with 64 or 256 MD CT scanners (Revolution GSI, GE Healthcare; Revolution CT, GE Healthcare, IL, USA). (Figure 1) Calcification scoring was performed by surgeons who were unaware of the patient's perioperative course. The degree of orifice stenosis due to calcification was scored as follows: patent, 0; partial occlusion, 1; or complete occlusion, 2. We defined "patent" as <50% stenosis in both axial and sagittal planes. Partial occlusion was defined as >50% stenosis in either axial or sagittal planes, whereas complete occlusion was defined as 100% stenosis in both axial and sagittal planes.

Statistical analysis: Statistical analysis was performed using SPSS Statistics version 19 (IBM, Ehningen, Germany). Kaplan–Meier long-term survival curves were generated as stratified by the calcification scores of CA and SMA orifices. Additionally, the Wilcoxon test was performed to compare survival between patient groups.

RESULTS

Preoperative patient characteristics are summarized in Table 1. (Table 1) The average patient age was 67.9 years. The most common cause of dialysis initiation was diabetic nephropathy ($N = 54$), followed by chronic glomerulonephritis ($N = 11$), and nephrosclerosis ($N = 4$). The median dialysis duration was 2276 (range, 8–17575) days. The average EuroSCORE II of the NOMI group was 25.6 ± 17.7 , which was significantly greater than that of the non-NOMI group (10.5 ± 12.5 ; $P = 0.046$). Seven patients in the NOMI

group and 51 patients in the non-NOMI group had extracardiac arteriopathies, such as peripheral artery disease, cerebral artery disease, and carotid artery stenosis. A significant difference ($P = 0.033$) was found in the prevalence of peripheral artery disease between the NOMI and non-NOMI groups. However, no difference was noted in the preoperative cardiac function between the two groups.

The operative procedures undergone by the patients are summarized in Table 2. (Table 2) Thirty-four patients underwent isolated coronary artery bypass grafting (CABG), 58 patients underwent valve surgery $\pm$ CABG, and 13 patients underwent aortic $\pm$ valve surgery or CABG. The incidence of NOMI was significantly high among patients who underwent aortic surgery ($P = 0.001$). All patients were completely followed up with a mean duration of 604 ± 585 days. Across all patients, the 30-day and in-hospital mortality rates were 13% and 18%, respectively. Eight patients experienced NOMI, and they all died in the hospital, six of whom died within 30 days after the operation.

The correlation between the calcification score and NOMI status is summarized in Figure 2. (Figure 2) The calcification scores of the SMA orifice were not significantly different between the two groups (NOMI 1.38 ± 0.52 vs. non-NOMI 1.13 ± 0.69 ; $P = 0.247$), but those of the CA orifice were significantly higher in the NOMI group (NOMI 1.63 ± 0.52 vs. non-NOMI 1.15 ± 0.65 ; $P = 0.039$). Additionally, the sum of the CA and SMA (CA + SMA) orifice calcification scores was significantly higher in the NOMI group (NOMI 3.00 ± 0.76 vs. non-NOMI 2.25 ± 1.18 ; $P = 0.028$).

The mortality rates were verified using Kaplan–Meier long-term survival curves and described in Figure 3. (Figure 3) The mortality rate was not significantly different among patients stratified by the SMA orifice calcification scores ($P = 0.477$), but that among patients stratified by the CA orifice calcification was significantly low depending on the score ($P = 0.040$). To investigate the relationship between mortality and abdominal artery calcification, we analyzed the sum of CA + SMA orifice calcification scores. (Figure 4) Patients with a high CA + SMA orifice calcification score showed no significant association with mortality ($P = 0.175$). In patients with CA + SMA orifice calcification score of 2, the combination pattern of "one patent artery orifice and another totally occluded" was not found. Therefore, a score of 0–1 meant that a patient had at least one non-occluded CA and SMA orifice, whereas a score of 3–4 indicated that a patient had at least one completely occluded CA and SMA orifice. Scores 0–1 vs. 2–4 and 0–2 vs. 3–4 were compared and described in Figure 4B and 4C, respectively. Patients with a high calcification score of the CA + SMA orifice tended to have a shorter long-term survival than patients without calcification.

DISCUSSION

This study has some crucial findings: Calcification of CA and SMA orifices in hemodialysis patients is (1) a risk factor for postoperative NOMI and (2) a poor prognostic factor for survival after cardiac surgery.

Table 1. Preoperative characteristics of patients

	>All patients (N = 100)	NOMI (N = 8)	Non-NOMI (N = 92)	P-value
Age, average (years)	69 (41-85)	73 (43-83)	69 (41-85)	0.530
Sex (female) (%)	48	3 (37.5%)	45 (48.9%)	0.717
Body mass index, average	22.81	21.6 (± 3.8)	22.9 (± 4.2)	0.390
Smoking status (%)	42	1 (12.5%)	41 (44.6%)	0.135
Current smoker	14	0 (0%)	14 (15.2%)	0.596
Past smoker	28	1 (12.5%)	27 (29.3%)	0.436
Comorbidities				
Hypertension	72	5 (62.5%)	67 (72.8%)	1.000
Diabetes mellitus (%)	60	4 (50.0%)	54 (54.8%)	0.717
Management: diet (%)	20	2 (25.0%)	18 (19.6%)	0.659
Management: drug (%)	20	1 (12.5%)	19 (20.7%)	1.000
Management: insulin (%)	20	1 (12.5%)	19 (20.7%)	1.000
Dyslipidemia (%)	47	5 (62.5%)	42 (45.7%)	0.469
Chronic lung disease (%)	9	1 (12.5%)	8 (8.7%)	0.543
Liver disease (%)	2	0 (0%)	2 (2.2%)	1.000
Extracardiac arteriopathy (%)	58	7 (87.5%)	51 (55.4%)	0.134
Peripheral artery disease (%)	50	7 (87.5%)	43 (46.7%)	0.033
Past medical history				
Stroke (%)	20	1 (12.5%)	19 (20.7%)	1.000
Percutaneous coronary intervention (%)	31	3 (37.5%)	28 (30.4%)	0.700
Previous cardiovascular surgery (%)	16	4 (50.0%)	12 (13.0%)	0.021
Cardiac status				
Left ventricular ejection fraction, average	48.8	42.0 (± 19.8)	49.6 (± 15.1)	0.322
New York Heart Association functional classification, average	2.21	2.13 (± 1.13)	2.22 (± 1.09)	0.828
Atrial fibrillation (%)	19	2 (25.0%)	17 (18.5%)	0.645
Dialysis				
Reason for dialysis				
Diabetic nephropathy (%)	56	4 (50.0%)	52 (56.5%)	0.728
Chronic glomerulonephritis (%)	11	0 (0%)	11 (12.0%)	0.593
Nephrosclerosis (%)	4	1 (12.5%)	3 (3.3%)	0.287
Duration, average (days)	2276 (8–17575)	2692 (230–9997)	2250 (8–17575)	0.248
Emergency operation (%)	28	2 (25.0%)	26 (28.3%)	1.000
EuroSCORE II, average	11.74	25.6 (± 17.7)	10.5 (± 12.5)	0.046

NOMI, nonocclusive mesenteric ischemia

Studies on the relationship between preoperative dialysis-dependent chronic renal failure and post-cardiac surgery NOMI: Previous studies on the relationship between dialysis and post-cardiac surgery NOMI risk have not provided consistent results. Sakamoto et al. reported that preoperative dialysis is a risk factor of NOMI in the perioperative period, although some reports do not consider

preoperative dialysis a risk factor [Sakamoto 2020]. Sato et al. reported that preoperative dialysis was not a risk factor for NOMI; by contrast, postoperative dialysis was a risk factor [Sato 2018]. They also found that high-dose norepinephrine, which was commonly used among hemodialysis patients after cardiac surgery, was a risk factor for NOMI [Groesdonk 2013; Klotz 2001; Sato 2018; Quiroga 2013]. However, according

Table 2. Operative procedure and follow-up status of the patient cohort

	All patients (N = 100)	NOMI (N = 8)	Non-NOMI (N = 92)	P-value
Operation				
Isolated CABG (%)	34	1 (12.5%)	33 (%)	0.259
OPCAB (%)	13	1 (12.5%)	12 (%)	1.000
Valve ± CABG (%)	58	3 (37.5%)	55 (%)	0.275
Aorta ± CABG ± valve (%)	13	5 (62.5%)	8 (%)	0.001
CPB time (min), average	148.8	166.9 (±104.1)	146.9 (±95.5)	0.614
Aorta clamp time (min), average	93.8	117.9 (±72.9)	91.8 (±70.2)	0.358
Mortality (30 days) (%)	13	6 (75.0%)	7 (7.6%)	<0.01
Mortality (30 days + in hospital) (%)	18	8 (100%)	10 (10.9%)	<0.01
Follow-up duration (days), average	595.8 (±582.6)	25.4 (3–88)	645.9 (5–2023)	<0.01
Death after discharge (%)	36	0 (0%)	36 (39.1%)	<0.01

CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; NOMI, nonocclusive mesenteric ischemia; OPCAB, off-pump CABG

Table 3. Calcification of the superior mesenteric and celiac arteries

	All patients (N = 100)	NOMI (N = 8)	Non-NOMI (N = 92)	P-value
CA, average	1.19	1.63 (±0.52)	1.15 (±0.65)	0.039
SMA, average	1.15	1.38 (±0.52)	1.13 (±0.69)	0.247
CA + SMA, average	2.31	3.00 (±0.76)	2.25 (±1.18)	0.028

CA, celiac artery; NOMI, nonocclusive mesenteric ischemia; SMA, superior mesenteric artery

to those reports, whether preoperative dialysis is a risk factor of NOMI remains controversial.

The present retrospective study only reviewed chronic dialysis patients undergoing cardiac surgery. Therefore, this study could not address whether preoperative chronic dialysis would be a risk factor for the postoperative incidence of NOMI. However, the occurrence rate of NOMI was 8%. It was higher than that of non-dialysis patients in previous reports [Klotz 2001; Sakamoto 2020]. Thus, the present study suggests that careful postoperative treatment, considering the possibility of NOMI, is needed for chronic dialysis patients undergoing cardiac surgery.

Evaluation method of CA/SMA orifice calcification: We used a CT-based scoring system, examined the calcification of the orifices of abdominal blood vessels (CA and SMA), and applied a three-level ordinal scale. By contrast, Juif et al. measured calcifications of the aorta, CA, SMA, and iliac artery in NOMI using the Agatston method, which generally is used in the quantitative assessment of coronary artery calcification [Juif 2021; Agatston 1990]. Moreover, Terlouw et al. reported abdominal artery calcification scoring using the Agatston definition for chronic mesenteric ischemia. Their mesenteric artery calcium score could identify chronic mesenteric ischemia with very high sensitivity and discriminative

ability [Terlouw 2021; Terlouw 2021]. Although the Agatston method was more objective and quantitative than our method, it required great time and effort; thus, we consider the Agatston method unsuitable in daily practice. By contrast, our scoring method is remarkably simple, and we believe that it could help assess the NOMI risk in dialysis patients undergoing cardiac surgery in daily practice.

Diagnostic difficulties of NOMI: Various studies have investigated NOMI as it is exceedingly difficult to diagnose and treat. Koltz et al. reported that selective angiography of the mesenteric artery is an effective diagnostic and treatment approach for NOMI [Klotz 2001]. Pérez-García et al. also reported that measuring the maximum diameter of the SMA—immediately inferior to the first branch—by CT was helpful for the diagnosis of NOMI [Pérez-García 2018]. In the present study, the diagnosis of NOMI was made by either CT angiography, followed by autopsy or surgical laparotomy, and NOMI in our patients was considered at a very advanced stage. Furthermore, several studies have reported that the mortality rate of NOMI after cardiac surgery is very high, ranging from 22% to 77%; thus, early recognition of the possibility of NOMI is very important [Groesdonk 2013; Sakamoto 2020; Sato 2018]. If risk factors were known before the operation, we could perform an aggressive examination,

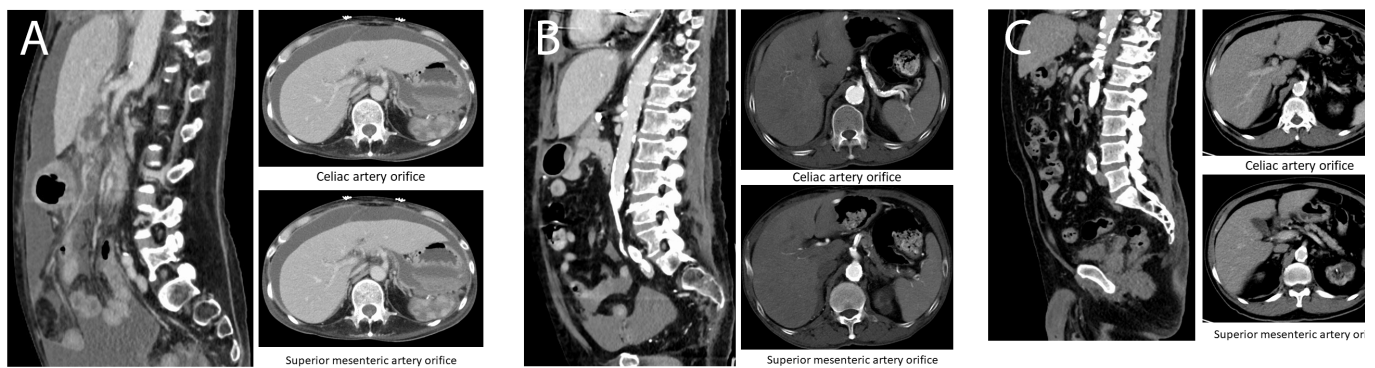


Figure 1. Calcification of the superior mesenteric artery orifice. The superior mesenteric artery orifice calcification was assessed by computed tomography and graded in three levels, which are as follows: (A) 0, patent; (B) 1, partial occlusion; and (C) 2, complete occlusion. (Left) sagittal view; (right) coronal view.

and the pretest probability could increase in case of suspicious symptoms and findings. Thus, our study may provide information on the risk factors of NOMI development in dialysis patients undergoing cardiac surgery.

Association of calcification score with postoperative NOMI: Although the SMA scores were not different, this study showed that the CA and CA + SMA scores were significantly higher in the NOMI group. By contrast, Juif et al. reported that abdominal atherosclerosis, especially in the SMA, is associated with poorer outcomes in NOMI [Juif 2021]. Majority of the blood flow for the mesentery is supplied by the SMA; thus, our findings should carefully be interpreted. We suppose that the difference between our findings and those of Juif et al. was due to the different evaluation methods used. Our evaluation method is very simple, but obtaining an exact quantification is difficult. Therefore,

to overcome this, we evaluated the calcification of CA/SMA orifices together. Our results suggest that calcification of CA/SMA orifices was significantly associated with the postoperative occurrence of NOMI, and it could be added to the risk estimation score in the future.

Calcification and long-term survival: A previous study using simple X-ray imaging showed that abdominal artery calcification is significantly associated with both all-cause and cardiovascular mortalities in hemodialysis patients, which is consistent with the results of the present study [Okuno 2007]. Therefore, we examined the long-term survival of dialysis patients stratified by the calcification score of CA and SMA orifices with Kaplan–Meier survival curves. Regarding the relationship between the calcification score and NOMI occurrence, mortality was shown to be significantly low depending on the CA orifice calcification score, whereas the mortality rate did not differ among patients with varying SMA orifice calcification scores. Furthermore, we examined the survival rates by calculating the CA + SMA orifice calcification score in some conditions using Kaplan–Meier survival curves to identify high-risk patients undergoing cardiac surgery. Results stratified according to CA + SMA orifice calcification scores were not significantly different, but patients with patent CA, SMA, or

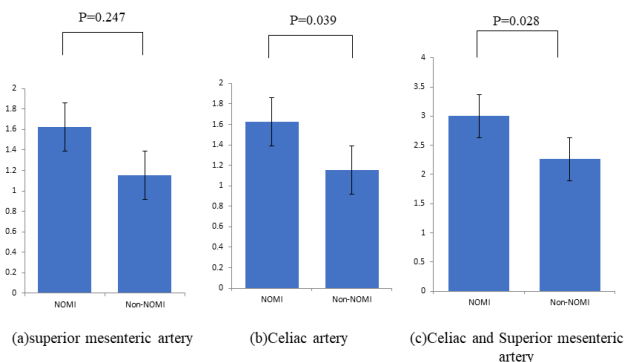


Figure 2. The comparison of NOMI with non-NOMI on the (A) superior mesenteric artery and (B) celiac artery. (C) The sum of the superior mesenteric artery and celiac artery orifice calcification scores is summarized. The SMA calcification scores were not significantly different between the two groups (NOMI 1.38 ± 0.52 vs. non-NOMI 1.13 ± 0.69 ; $P = 0.247$), but the CA calcification score was significantly higher in the NOMI group (NOMI 1.63 ± 0.52 vs. non-NOMI 1.15 ± 0.65 ; $P = 0.039$). In addition, the sum of the SMA and CA calcification scores was significantly higher in the NOMI group (NOMI 3.00 ± 0.76 vs. non-NOMI 2.25 ± 1.18 ; $P = 0.028$). CA, celiac artery; NOMI, nonocclusive mesenteric ischemia; SMA, superior mesenteric artery

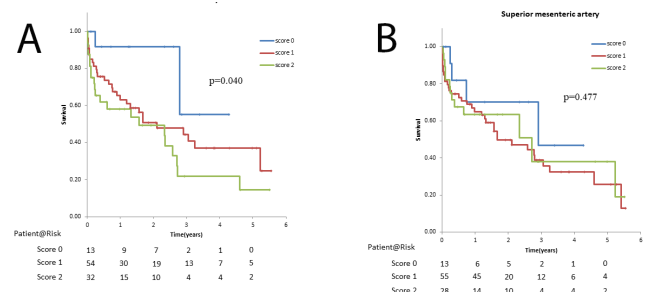


Figure 3. Kaplan–Meier survival curve showing the association of the orifice of the (A) superior mesenteric artery and (B) celiac artery calcification score with long-term survival. Patients with (B) superior mesenteric artery orifice calcification were not significantly different ($P = 0.460$). By contrast, patients with celiac artery orifice calcification had significantly worse long-term survival ($P = 0.040$).

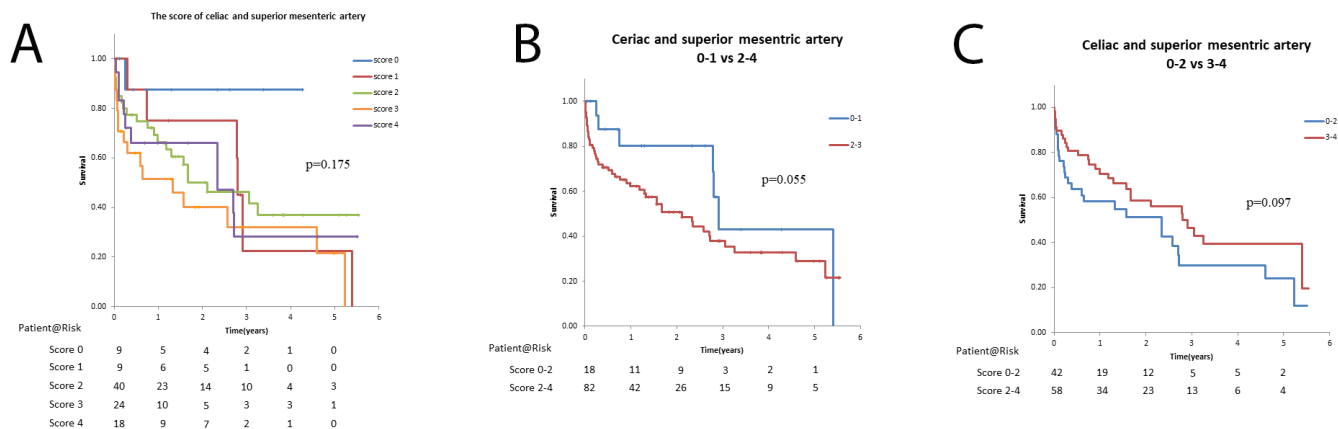


Figure 1. Calcification of the superior mesenteric artery orifice. The superior mesenteric artery orifice calcification was assessed by computed tomography and graded in three levels, which are as follows: (A) 0, patent; (B) 1, partial occlusion; and (C) 2, complete occlusion. (Left) sagittal view; (right) coronal view.

both, i.e., score 0 or 1, tend to have a longer long-term survival ($P = 0.055$). Otherwise, patients with totally calcified CA, SMA, or both, i.e., score 3 or 4, tend to have a shorter long-term survival ($P = 0.097$). Although this finding failed to demonstrate a significant difference, it may suggest that the patients with high CA + SMA orifice calcification scores tended to have shorter long-term survival than patients without calcification. Long-term and more detailed validation may provide an accurate risk assessment and insight into the indications of dialysis patients for cardiac surgery. As the number of long-term hemodialysis patients is expected to increase due to improved dialysis management, it is crucial to understand and assess the risks of cardiac surgery in dialysis patients.

Study limitations: The main limitations of this study were the small number of cases assessed, different types of surgeries performed, and heterogeneous perioperative date between the two groups. Furthermore, CT-based calcification scoring was performed by surgeons, and the evaluation was based on an interval scale. The results might have been different if the analysis had been performed using a well-established method to quantify calcification, such as the Agatston definition [Juif 2021; Terlouw 2021; Terlouw 2021]. Nevertheless, we consider that the methods for preoperative risk assessment should be simple and easy to use in daily clinical practice.

Finally, this study focused on calcification in CA and SMA orifices and was not adjusted for preoperative risk assessment, surgical factors, or postoperative management factors. Further large volume studies are mandatory to confirm the relationship between the calcification of CA/SMA and NOMI after cardiac surgery.

CONCLUSION

This study demonstrated that calcification of CA and/or SMA orifices was associated with postoperative NOMI and poor long-term outcomes among dialysis patients undergoing cardiac surgery.

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