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Prognostic Impact of Multivessel Disease on Long-Term Survival After Major Lower Limb Amputations: A Cohort Study

Simão Almeida Oliveira

M

2024

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DESIGNAÇÃO DA ÁREA DO PROJECTO

Ciências médicas e da saúde

TÍTULO DISSERTAÇÃO/~~MONOGRAFIA~~ (riscar o que não interessa)

Prognostic Impact of Multivessel Disease on Long-Term Survival After Major Lower Limb Amputations: A Cohort Study

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ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
É AUTORIZADA A REPRODUÇÃO PARCIAL DESTE TRABALHO (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
DE ACORDO COM A LEGISLAÇÃO EM VIGOR, (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTE TRABALHO.	☒

Faculdade de Medicina da Universidade do Porto, 14 / 03 / 2025

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UC Dissertação - DECLARAÇÃO DE TRANSPARÊNCIA RELATIVAMENTE À UTILIZAÇÃO DE FERRAMENTAS DE CHATBOT GENERATIVO BASEADAS EM LARGE LANGUAGE MODELS

Eu, Simão Almeida Oliveira, abaixo assinado, nº mecanográfico 201905159, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro que:

☒ Não procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* para nenhuma das tarefas no contexto do meu trabalho de Dissertação ou Monografia

☐ Procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia, encontrando-se todas as interacções (*prompts* e respostas) transcritas em anexo bem como a indicação das aplicações utilizadas.

Neste sentido, confirmo que a eventual utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia foi exclusivamente descrita na sequência de *prompts* e respostas transcritos em anexo e nas aplicações indicadas.

Faculdade de Medicina da Universidade do Porto, 14/03/2025

Assinatura conforme cartão de identificação:
Simão Almeida Oliveira

Prognostic Impact of Multivessel Disease on Acute Lower Limb Ischemia Patients: A Cohort Study

Journal:	*Science Progress*
Manuscript ID	SCI-25-0179
Manuscript Type:	Original Research Article
Date Submitted by the Author:	25-Jan-2025
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Keywords:	acute peripheral ischemia, atrial fibrillation, cardiovascular disease, embolectomy, postoperative morbidity, postoperative mortality
Abstract:	Acute lower limb ischemia (ALI) is closely linked to conditions like diabetes mellitus and peripheral arterial disease, as well as the presence of polyvascular disease (PVD). The present study aimed to evaluate the impact of PVD on perioperative outcomes in patients with ALI. Among 161 patients, these were categorized into subgroups based on their PVD status: control (N=81), PVD1 (single arterial bed involvement) (N=61), and PVD2 (coronary and cerebrovascular) (N=18). Descriptive statistics and univariate analysis were performed. The mean age was 71.17±11.6. Higher prevalences of diabetes mellitus (n=21, 33.9% in PVD1; n=8, 44.4% in PVD2) and hypertension (n=55, 88.7% in PVD1; n=16, 88.9% in PVD2) were reported for the PVD groups, when comparing to controls, who registered 13 (16.0%) and 41 (50.6%) individuals, respectively. Anticoagulant therapy and acute myocardial infarction were more common in the PVD1 and PVD2 groups (p=0.005 and p=0.001). Non-cardiovascular mortality rates were significantly higher in the PVD groups, with 24.2% in PVD1 and 33.3% in PVD2 compared to 11.1% in the control group (p = 0.033). The study concluded that PVD significantly

	impacts the status of ALI patients, emphasizing the need for tailored, multidisciplinary care.

Prognostic Impact of Multivessel Disease on Acute Lower Limb Ischemia Patients: A Cohort Study.

Running title: Multivessel Disease and Acute Limb Ischemia

Original research article

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Keywords: acute peripheral ischemia; atrial fibrillation; cardiovascular disease; embolectomy; postoperative morbidity; postoperative mortality.

Word count: 4222 (abstract and references); 3502 (manuscript and abstract)

Abstract:

Acute lower limb ischemia (ALI) is closely linked to conditions like diabetes mellitus and peripheral arterial disease, as well as the presence of polyvascular disease (PVD). The present study aimed to evaluate the impact of PVD on perioperative outcomes in patients with ALI. Among 161 patients, these were categorized into subgroups based on their PVD status: control (N=81), PVD1 (single arterial bed involvement) (N=61), and PVD2 (coronary and cerebrovascular) (N=18). Descriptive statistics and univariate analysis were performed. The mean age was 71.17±11.6. Higher prevalences of diabetes mellitus (n=21, 33.9% in PVD1; n=8, 44.4% in PVD2) and hypertension (n=55, 88.7% in PVD1; n=16, 88.9% in PVD2) were reported for the PVD groups, when comparing to controls, who registered 13 (16.0%) and 41 (50.6%) individuals, respectively. Anticoagulant therapy and acute myocardial infarction were more common in the PVD1 and PVD2 groups (p=0.005 and p=0.001). Non-cardiovascular mortality rates were significantly higher in the PVD groups, with 24.2% in PVD1 and 33.3% in PVD2 compared to 11.1% in the control group (p = 0.033). The study concluded that PVD significantly impacts the status of ALI patients, emphasizing the need for tailored, multidisciplinary care.

Introduction

Acute lower limb ischemia (ALI) has been inherently associated with the prevalence of conditions such as diabetes mellitus and peripheral arterial disease. Diabetes mellitus has been shown to be present in at least 49.1% of patients diagnosed with ALI (1). Overall, ALI patients' prognosis underlies a significant risk of combined death and amputation, with recent data reporting a 15-20% risk at 30 days, escalating to a 50-60% risk at the 1-year mark.(2)

One of the most important prognostic factors is the presence of multivessel disease, which can be defined as the presence of significant atherosclerosis in peripheral and/or coronary arteries (3), this way becoming an excellent indicator for systemic vascular health and reflecting not only on the presence of widespread atherosclerosis as well as the compromise of the overall cardiovascular function.(4)

According to the current epidemiological data, the prevalence of higher rates of ALI is especially correlated to elderly populations and those affected by comorbidities such as multivessel disease. In a study conducted in Japan, regarding 531 patients diagnosed with ALI, its incidence significantly increased with the aging of patients, as only 19.2% of individuals being under 65 years of age, while 27.9% were aged over 80 years.(5) Additionally, another study, conducted in the context of EUCLID (Examining Use of Ticagrelor in Peripheral Artery Disease), analysed 13885 individuals with PAD, reporting 232 (1.7%) to have been hospitalized in the context of ALI, stating this condition to be associated with limb morbidity.(6) Such conditions end up compromising not only the normal function of the circulatory system and the viability of these patient's limbs, as well as their day-to-day activities and overall quality of life (7).

The aim of this study is to assess the impact of multivessel disease on perioperative outcomes in patients with acute limb ischemia , specifically analyzing its influence on perioperative mortality, complication rates, and immediate postoperative recovery.

Methods

Study design and participants

This is a retrospective observational study involving 161 consecutive patients with acute lower limb ischemia admitted to the Department of Vascular Surgery from a tertiary referral hospital between January 2014 and November 2018.

A complete medical history, including information on prior treatment, was obtained from all participants and medical documentation. The diagnosis of ALI was based on established criteria: sudden onset of the symptoms in the prior 48 hours, presence of rest pain, sensory and mobility alteration and other symptoms of ALI. Computed tomography angiography (CTA) was performed to aid in complex revascularization planning and to resolve diagnostic uncertainties, providing detailed imaging data of each patient's vascular impairment and its impact on the affected area of ischemia. After surgery, all patients underwent a duplex ultrasound (DUS) to evaluate for multivessel disease, assess atherosclerosis, and determine the effectiveness of the procedure.

PVD is considered the presence of atherosclerotic disease in two or more arterial beds (8). The patients were divided into three different groups. The first group, serving as the control group, consisted of patients with no known atherosclerotic lesions. The second group included patients with ALI and a diagnosis of one condition among CVD, CAD or PAD (Polyvascular Disease 1, PVD1). The third group comprised patients with ALI and two out of three conditions: CVD, CAD and PAD (Polyvascular Disease 2, PVD2).

The present work follows the Strengthening the Reporting of Cohort Studies in Surgery Criteria (STROCCS) (9). The study protocol respects the Declaration of Helsinki and is under the European Union General Data Protection Regulation (GDPR). The study was approved by the university Bioethics Committee (no. 111/2020). The university Ethics Committee waived the requirement of obtaining informed consent from the patients.

Surgical treatment

All patients underwent surgical treatment using open, endovascular, or hybrid methods, or underwent primary amputation. The treatment approach for acute limb ischemia was determined based on the underlying cause (embolism or acute thrombosis) and the Rutherford classification of ischemia, guiding the use of direct thrombolysis, mechanical thrombectomy, or embolectomy. Revascularization was not performed in the case of Rutherford grade III, advanced limb ischemia/necrosis. In patients with major comorbidities who experienced significant improvement in their clinical condition following conservative treatment, surgical intervention was postponed to allow for elective preparation. Peripheral circulation played a critical role in determining the treatment approach. Due to the lack of peripheral blood flow in most patients, DCT was implemented. Restoring peripheral blood flow was an introduction to other procedures in case of significant stenosis, while treatment was discontinued if adequate circulation was achieved.

In most cases, limb open embolectomy or thrombectomy was performed under epidural or spinal anesthesia. For patients in whom these types of anesthesia were contraindicated, local anesthesia combined with sedation was used. Clots were removed using Fogarty catheter, both proximally and distally, until acceptable inflow and outflow

were achieved. An additional endarterectomy was performed in massive atherosclerotic plaques were present at the site of the arterial incision. The arteriotomy was closed with either a primary suture or patch angioplasty in case of a small arterial diameter. Patients without adequate inflow or outflow were considered eligible for bypass surgery. Fasciotomy was performed in cases of suspected subfascial edema.

Endovascular treatment

DCT and MTH were the first-choice endovascular methods for treating acute ischemia in all areas (10). Access was obtained via the common femoral or left radial artery. During DCT infusion, Alteplase (Actilyse-Boehringer-Ingelheim®) was administered at 1 mg/hour, preceded by a 5 mg bolus. UFH was simultaneously administered through the sheath at a rate of 500 IU/hour. Fibrinogen and APTT levels were monitored four times daily. DCT was discontinued early if the fibrinogen level dropped below 150 mg/dl (11). Control arteriography was performed before sheath removal.

For mechanical thrombectomy, the AngioJet® (Boston Scientific) and Rotarex® (Straub Medical) systems were used, with catheter diameters selected based on the size of the artery. If the procedure was deemed insufficient, DCT or PTA/stenting was performed as needed. The Spider embolic protection system (Medtronic) was employed in some lower limb arterial procedures.

Postoperatively, UFH was administered intravenously via infusion pump, targeting an APTT prolongation of 2.5-3 times the normal range. In case of simultaneous occlusion of the celiac trunk and superior mesenteric artery, efforts were made to open both arteries. DCT was used cautiously due to the known mechanism of endogenous thrombolysis occurring during intestinal ischemia [18].

Statistical analysis

The sample size for a survival test was calculated using online Sample Size Calculators for Designing Clinical Research (https://sample-size.net/sample-size-survival-analysis/), with a statistical power (β) of 80% and a significance level of 0.05. The sample was estimated (131) for a hazard ratio >2 between groups and a predicted survival at the end of follow-up of 80%, although higher event rate differences are described (4). Although bigger event rate disparities are stated, the sample was calculated at 147, with a hazard ratio of 1.6 (1.3 to 1.9) across groups (4, 12). A total estimated sample of 154 was collected with an expected loss-to-follow-up rate of 5%.

For statistical analysis, SPSS (IBM Corp., released 2023. IBM SPSS Statistics for Windows, version 29.0, Armonk, NY, USA) was used.

Categorical data are expressed as numbers of patients and percentages. The chi-square test or Fisher's exact test were used to compare proportions. Numeric variables were presented as medians and quartiles and compared using mainly ANOVA and Kruskal-Wallis H test when their distribution was not normal. In the context of survival analysis, the endpoint was defined as all-cause mortality.

Survival analysis was assessed using the Kaplan-Meyer estimator and lifetable method. Perioperative deaths were removed. Log-rank estimator was applied to compare time-dependent variables. Stratified analysis was conducted for PVD1 and PVD2 patients. Statistical tests were two-tailed, and p-values < 0.05 were considered significant. (Table 1)

Results:

This study has included a total of 161 participants, divided into three groups based on their vascular disease status: Control (N = 81), PVD1 (N = 62) and PVD2 (N = 18). The median follow-up period was 47 months 95% CI [42.9-51.1]. The mean age of participants differed significantly between the groups: 68.78 years (±11.713) in the Control group, 74.10 years (±11.206) in the PVD1 group, and 71.83 years (±10.629) in the PVD2 group ($p = 0.03$).

The prevalence of diabetes mellitus was significantly higher in the PVD1 (N= 21, 33.9%) and PVD2 (N=8, 44.4%) groups compared to the Control group (N=13, 16.0%, $p=0.009$). Similarly, hypertension was significantly more prevalent in the PVD1 (N=55, 88.7%) and PVD2 (N=16, 88.9%) groups compared to the Control group (N=41, 50.6%, $p < 0.001$).

The prevalence of atrial fibrillation (AF) was N=19 (23.5%) in the Control group, N=22 (35.5%) in the PVD1 group, and N=9 (50.0%) in the PVD2 group (p=0.056). Regarding the presence of emboli, it was recorded in N=29 (35.8%) of the Control group, N=30 (48.4%) of the PVD1 group, and N=9 (50.05%) of the PVD2 group (p=0.249), indicating that embolism did not have statistical significance in this study.

Anticoagulation status varied significantly: 12 (19.7%) of PVD1 and 7 (38.9%) of PVD2 patients were on anticoagulant therapy, compared to 7 (8.6%) in the Control group (p=0.05). Notably, within the PVD2 group, 2 patients (11.1%) with recorded embolism were not anticoagulated, and an additional 2 patients (11.1%) with AF had not yet initiated anticoagulant therapy.

The surgical interventions performed according to the PVD status (Table 2) indicate that the majority of participants in all groups underwent embolectomy or thrombectomy, with N=57 (70.4%) in the Control group, N=48 (77.4%) in PVD1, and

N=12 (66.7%) in PVD2, showing no significant statistical differences (p=0.536). Mechanical thrombectomy was performed in N=8 (9.9%) of patients in the Control group, N=7 (11.3%) in PVD1, and N=4 (22.2%) in PVD2, but this also did not reach statistical significance (p = 0.336). Primary amputation occurring in only two patients from the Control group (2.5%, p= 0.368).

In the surgical management of acute limb ischemia based on etiology, direct embolectomy/thrombectomy was the most common approach, performed in 50 (53.8%) of thrombotic cases and 67 (98.5%) of embolic cases. Primary amputation was extremely rare, occurring only in thrombotic cases (2 patients, 2.2%) (Table 3).

The overall in -hospital mortality rates for each group were N=16 (19.8%) in the Control group, N=5 (8.1%) in PVD1, and N=0 in PVD2 (p=0.026). Secondary amputations occurred in N=17 (21%) of patients in the Control group, N=18 (29%) in the PVD1 group, and only N=2 (11.1%) of PVD2 group (p=0.235) (Table 4).

Cardiovascular and all-cause mortality rates showed no statistically significant differences among the groups (log-rank p=0.100 and p=0.785, respectively), with survival rates remaining relatively high in all groups. However, significant differences were observed in non-cardiovascular mortality (log-rank p=0.033). By 36 months, survival declined to 87.4% in the Control group, 76% in PVD1, and 72.2% in PVD2 (Figure 1). The hazard ratio was 1.840 95% CI (1.141-2.967, P=0.012).

Discussion

The study revealed significant demographic and clinical heterogeneity among the groups. Patients in the PVD1 and PVD2 groups were older and had a higher prevalence of diabetes mellitus and hypertension compared to the Control group. Notably, anticoagulant therapy was significantly more frequent in the PVD2 group.

Cardiovascular mortality was lower in PVD1 and PVD2 groups, whereas non-cardiovascular deaths were significantly more common in these groups compared to the Control group. AMI and ischemic stroke were significantly more prevalent in the PVD groups, underscoring the severity of their conditions. (Figure 2)

When comparing mortality outcomes in this study, it is notable that as the PVD status worsened, non-cardiovascular death rates increased. The differences in mortality rates, when stratified by PVD status, suggest that the presence of PVD increases the likelihood of patients being on anticoagulant therapy or undergoing percutaneous interventions, which may lower their cardiovascular death risk (14).

Mok et al. and Konig et al. respectively highlighted the association between PAD and a higher prevalence of infectious diseases, and well as the correlation between chronic kidney disease and PVD. These findings support the idea that patients with PVD face increased risks of systemic hazards like infections, renal failure and metabolic imbalances, leading to higher non-cardiovascular death rates compared to the Control group (13, 15).

This study also suggests that PVD is associated with higher rates of both ischaemic stroke and AMI. These findings reflect the increased risk of thromboembolic events and heightened vulnerability to cardiovascular complications in patients with progressively advanced polyvascular impairment. This is consistent with the findings of Baumann et al. and Saito et al., who reported that PVD was a complicating factor in 40% to 70% of AMI cases in their studies (16, 17).

PVD has also been established as a solid predictor of mortality, particularly non-cardiovascular death. Specifically, individuals with PVD are more prone to suffering from a range of cardiovascular conditions, such as ischaemic events, due to compromised

vascular reserve, microcirculatory deficiencies and overall issue and organ perfusion. This data is corroborated by Aday et al., whose study reported not only a higher risk of AMI, stroke, and sudden cardiac death, but also emphasized the role of microvascular disease and chronic limb ischemia in the pathophysiology of both PAD and PVD (18). Patients with PVD are also more likely to be affected by conditions such as systemic atherosclerosis, which, when combined with the previously mentioned risk factors, contributes to the development of chronic hypoxia and compromised vascular function This, in turn, leads to increased rates of postoperative mortality among individuals with PVD (19). In this regard, Subwerhal et al. noted that presence of PVD is directly associated with systemic atherosclerosis, which, for example, increases the risk for ischemic events and overall greater vascular burden, findings that align with those of our study.

Additionally, patients with PVD reported high prevalences of heart failure, although this data did not reach statistical significance (p=0.058). This is likely associated with coronary artery disease (CAD), which is the primary risk factor for developing heart failure in these individuals. In fact, this finding has been observed in other studies, such as those by Velagaleti et al., who reported that CAD could account for up to 73% of patients suffering from heart failure.(20). Since CAD has strong collinearity with PVD, this may explain why heart failure was not statistically significant in this study, despite its high prevalence among PVD patients (21). Chunawala et al. found that the presence of PVD in individuals with both reduced and preserved ejection fraction heart failure significantly increased mortality rates in these patients, with rates of26% (CI: 1.07-1.50) and 29% (CI: 1.03-1.62) for each subgroup, respectively. This reflects the higher likelihood of individuals with PVD likely having pre-existing conditions, such as heart failure.(22)

Finally, when analysing the results for the presence of AF, this parameter was found to be borderline statistically significant (p=0.056). This could be because, although AF is associated with significant cardiovascular impairment in those with PVD (23), it is less impactful than other risk factors, such as systemic atherosclerosis, hypertension, or diabetes mellitus, when specifically considering its association with PVD. AF may also contribute to the observed mortality, as it has been identified as a significant risk factor in patients with peripheral vascular disease, further complicating their clinical outcomes and increasing the likelihood of adverse events (24), thereby diminishing the role of PVD in predicting long-term all-cause mortality.

Most non-cardiovascular deaths in the cohort were attributed to cancer, predominantly lung and breast cancer, which likely explains the higher mortality observed in the PVD1 and PVD2 groups. Several studies support the observation that non-cardiovascular deaths, particularly from lung and breast cancers, contribute significantly to higher mortality rates in patients with vascular disease (25). For instance, research indicates that lung cancer patients often present with multiple comorbidities, such as chronic obstructive pulmonary disease (COPD), diabetes, and congestive heart failure, which adversely affect survival outcomes (25). Additionally, some patients were reported to have pneumonia as the cause of death; however, it is plausible that underlying comorbidities contributed significantly to their mortality, highlighting the multifactorial nature of their clinical decline.

One of the limitations of the study is the small size of the study group. Although patients with varying degrees of vascular impairment, there was still an uneven distribution of patients across the three subgroups (Control, PVD1 and PVD2). Moreover, all patients were treated and followed in a single high-volume tertiary care center, which could affect the external validity of the results. Other limitations include the lack of data

on non-anticoagulant/antiplatelet therapies at the time of admission, factors that could influence postoperative outcomes. Furthermore, the fact that the outcomes reported were measured within a 30-day timeline restricts the ability to generalize findings to a longer-term analysis.

Finally, the lack of detailed information on the postoperative period, including data on ischemic events during the follow-up and other factors such as patient adherence to therapy and rehabilitation progress, underscore the need for follow-up studies with broader data collection. This study should aim to evaluate the long-term survivability and the progression of morbidity and mortality rates within this population. Patients who were directly referred to end-of-life and palliative care were most likely those with higher PVD scores, which may have introduced selection bias. Additionally, conducting sensitivity analyses was not feasible in this study.

Further studies focusing more on long-term complications and therapeutic measures are needed to strengthen the findings of this study. Such research should aim to evaluate more effective therapeutic interventions, develop faster and more efficient screening techniques, and ultimately provide a better long-term prognosis for patients with PVD, exposed to acute limb ischemia.

Additionally, implementing a multidisciplinary care model could enhance the assessment of each patient´s overall vascular impairment and associated comorbidities, such as hypertension, diabetes mellitus. This approach could not only improve the vascular viability of the affected limbs but also advance screening and treatment strategies for hazardous outcomes reported in this study, including AMI and ischemic stroke.

Conclusion:

PVD represents a major risk factor for both cardiovascular and non-cardiovascular death, as well as a multitude of associated complications in patients undergoing major lower-limb amputations, primarily due to the underlying acute limb ischemia. The results suggest that measures such as an optimized prescription of anticoagulant drugs and the use of revascularization techniques could improve the systemic cardiovascular function in these patients. However, as indicated by the high non-cardiovascular death rates observed, a multidisciplinary approach would be the most effective way to enhance postoperative quality of life and event-free survival of these patients.

Acknowledgements

The authors have no acknowledgements to declare.

Conflict of Interest Statement

Mariana Fragao Marques is an employee of Novo Nordisk.

Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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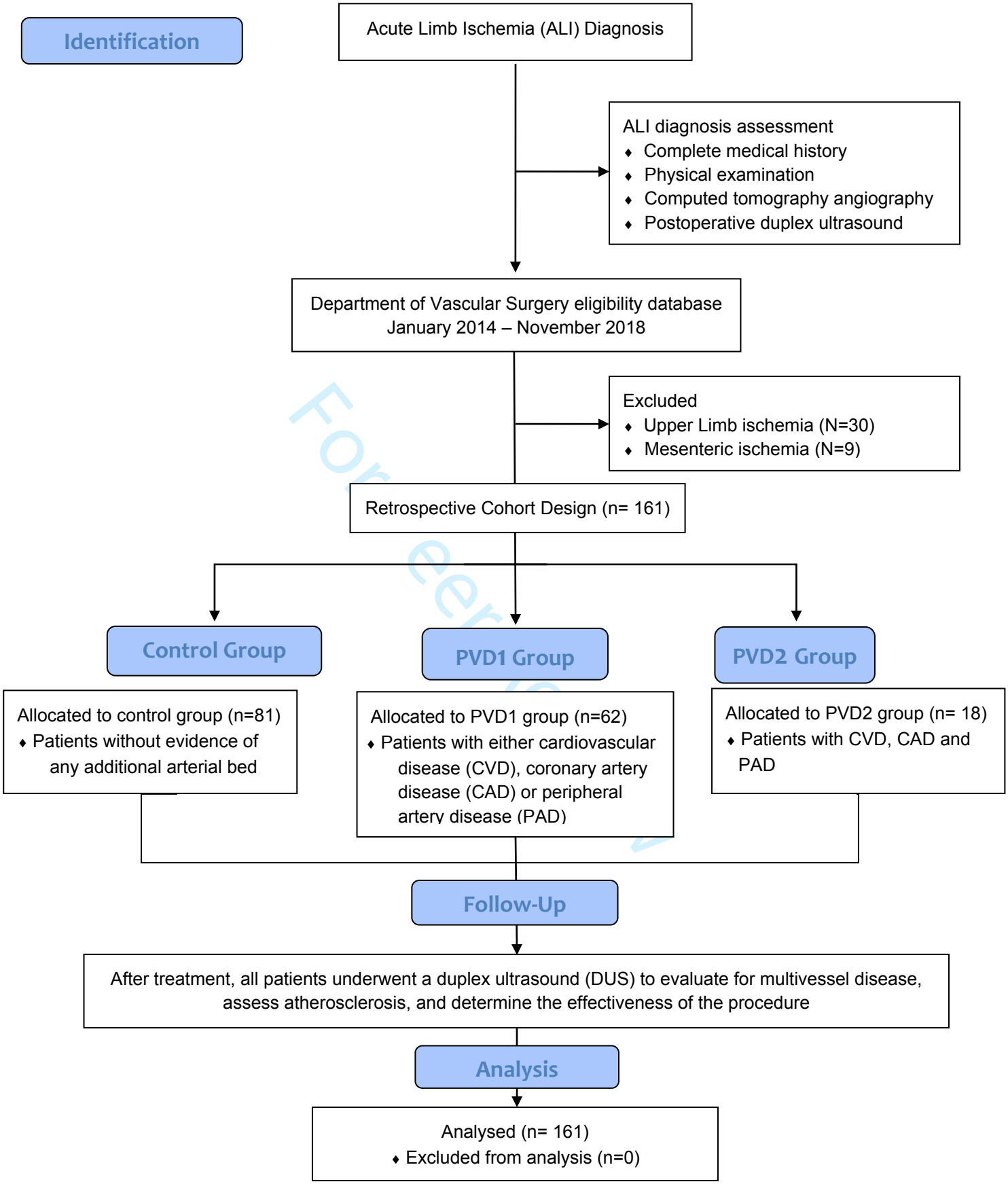
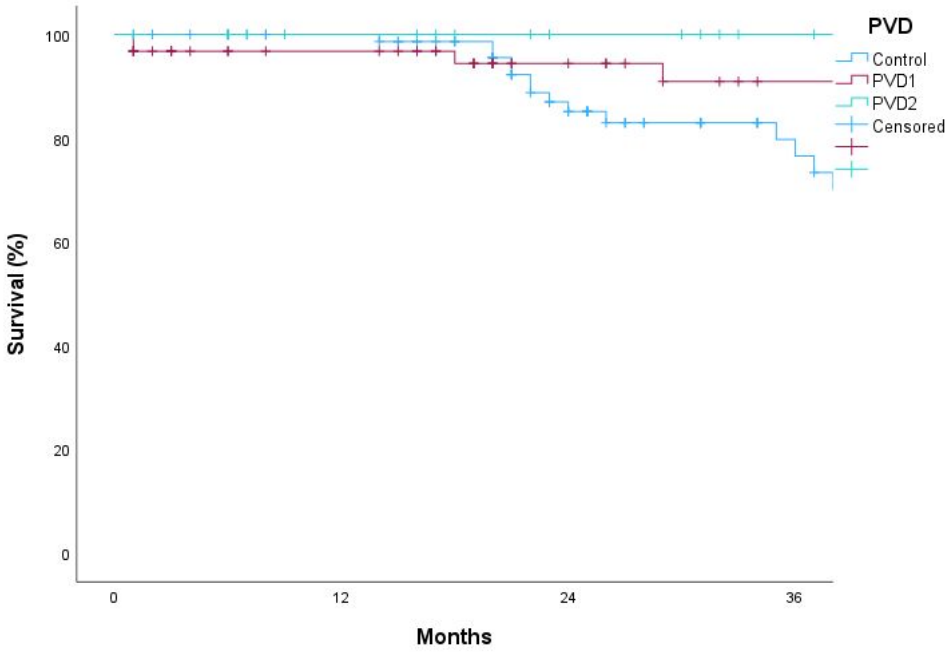


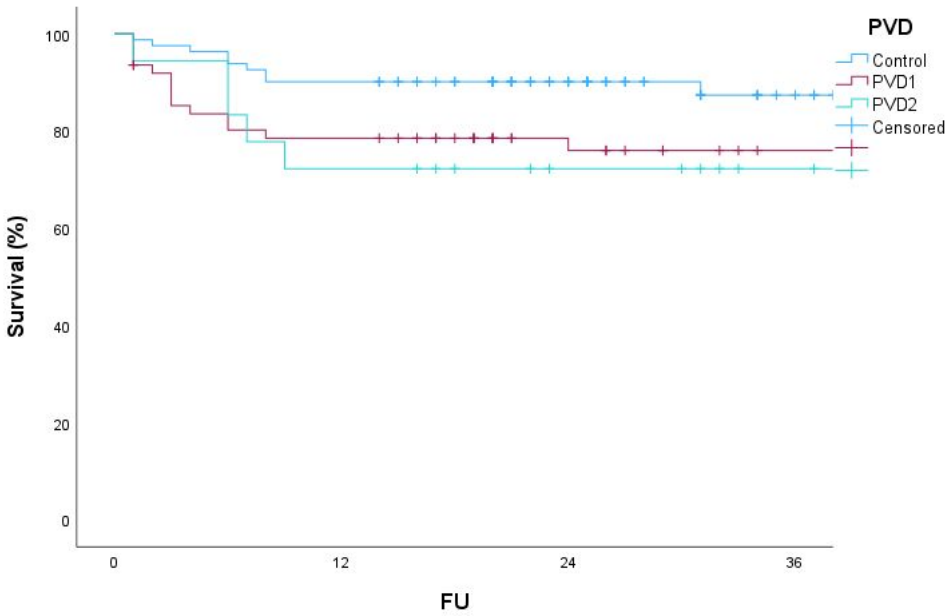
Figure 1 – Flow diagram

Figure 2.A. Cardiovascular Mortality



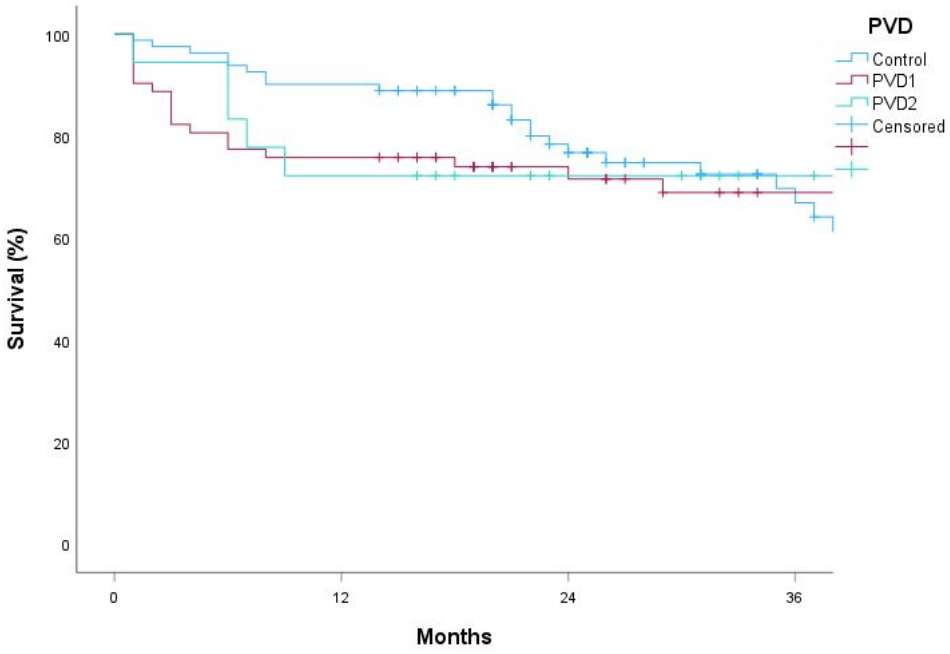
Cardiovascular Mortality Log rank p=0.100		30d	12	24	36
Control	% SE (%) Cases Nº at risk	100 0 0 80	100 0 0 80	85.1 4.6 9 44	76.6 6.3 12 24
PVD1	% SE (%) Cases Nº at risk	96.8 2.2 2 56	96.8 2.2 2 47	94.4 3.2 3 30	90.9 4.6 4 22
PVD2	% SE (%) Cases Nº at risk	100 0 0 17	100 0 0 13	100 0 0 8	100 0 0 4

2.B. Non-Cardiovascular Mortality



Non-Cardiovascular Mortality Log rank p=0.033		30d	12	24	36
Control	% SE (%) Cases Nº at risk	98.8 1.2 1 80	90.1 3.3 8 73	90.1 3.3 8 44	87.4 4.2 9 24
PVD1	% SE (%) Cases Nº at risk	93.5 3.1 4 56	78.5 5.3 13 47	76 5.7 14 30	76 5.7 14 22
PVD2	% SE (%) Cases Nº at risk	94.4 5.4 1 17	72.2 10.6 5 13	72.2 10.6 5 8	72.2 10.6 5 4

2.C. All-cause Mortality



All-cause Mortality Log rank p=0.785		30d	12	24	36
Control	% SE (%) Cases Nº at risk	98.8 1.2 1 80	90.1 3.3 8 73	76.7 5.0 17 46	66.9 6.4 21 24
PVD1	% SE (%) Cases Nº at risk	90.3 3.8 6 56	75.8 5.4 15 47	71.6 5.9 17 20	68.9 6.3 18 22
PVD2	% SE (%) Cases Nº at risk	94.4 5.4 1 17	72.2 10.6 5 13	72.2 10.6 5 9	72.2 10.6 5 4

Table 1 – Populations Characteristics and Demographics

	Control *N* = 81(%)	PVD1 *N* = 62(%)	PVD2 *N* = 18 (%)	*P*-value
Age (mean±SD)	68.78±11.713	(74.10±11.206)	71.83±10.629	0.03
Gender (Male)	50 (61.7)	32 (51.6)	8 (44.4)	0.281
Hyperlipidemia	16 (19.8)	15 (24.2)	7 (38.9)	0.222
Diabetes mellitus	13 (16.0)	21 (33.9)	8 (44.4)	0.009
Alcohol abuse	4 (4.9)	7 (11.3)	1 (5.6)	0.340
Smoking history	21 (25.9)	24 (38.7)	6 (33.3)	0.262
Hypertension	41 (50.6)	55 (88.7)	16 (88.9)	<0.001
CKD	20 (30.3)	19 (33.3)	6 (35.3)	0.897
CAD	0 (0.0)	49 (79.0)	16 (88.9)	<0.001 *
PCI	1 (1.2)	5 (8.1)	9 (50.0)	<0.001*
CABG	1 (1.2)	3 (4.8)	2 (11.1)	0.114 *
Heart failure	17 (21.0)	23 (37.1)	3 (16.7)	0.058
PAD	62 (76.5)	40 (64.5)	10 (55.6)	0.118
COPD	5 (6.2)	5 (8.1)	0 (0.0)	0.459
Carotid stenosis	0 (0.0)	0 (0.0)	7 (38.9)	<0.001*
Hemoglobin	12.8±2.1	12.5±2.44	12.0±1.9	0.281
AF	19 (23.5)	22 (35.5)	9 (50.0)	0.056
Paroxysmalt AF	4 (4.9)	6 (9.7)	2 (11.1)	0.464
Permanent AF	15 (18.5)	13 (21.0)	7 (38.9)	0.163
Persistent AF	0 (0.0)	3 (4.8)	0 (0.0)	0.087
Thrombus	52 (64.2)	32 (51.6)	9 (50.0)	0.249

Embolus	29 (35.8)	30 (48.4)	9 (50.0)	0.249
Anticoagulation status	7 (8.6)	12 (19.7)	7 (38.9)	0.05

AF – Atrial Fibrillation; CABG - coronary artery bypass grafting; COPD - chronic obstructive pulmonary disease; CKD - Glomerular filtration rate <60 ml/min; MTH - mechanical thrombectomy; PAD - peripheral artery disease; PCI - percutaneous coronary intervention; PVD – Polyvascular Disease; SD – Standard deviation; TIA - transient ischemic attack.

*Colinearity

Table 2. Surgical interventions according to polyascular disease status

	Control *N* =81(%)	PVD1 *N* =62(%)	PVD2 *N* = 18 (%)	*P*-value
Direct Embolectomy/Thrombectomy	57 (70.4)	48 (77.4)	12 (66.7)	0.536
Mechanical Thrombectomy	8 (9.9)	7 (11.3)	4 (22.2)	0.336
DCT	14 (17.3)	7 (11.3)	2 (11.1)	0.550
Primary Amputation	2 (2.5)	0	0	0.368

DCT - Direct Catheter Thrombolysis; PVD – Polyvascular Disease.

Table 3. Surgical approach according to etiopathogenesis

	Thrombotic ALI	Embolic ALI
Direct Embolectomy/Thombectomy	50 (53.8)	67 (98.5)
Mechanical Thrombectomy	18 (19.4)	1 (1.5)
DCT	23 (24.7)	0
Primary Amputation	2 (2.2)	0

ALI – Acute Limb ischemia; DCT - Direct Catheter Thrombolysis; PVD – Polyvascular Disease.

Table 4. Patient`s outcomes according to Polyvascular disease status.

	Control *N* = 81(%)	PVD1 *N* = 62(%)	PVD2 *N* = 18 (%)	*P*-value
Secondary Amputation	17 (21.0)	18 (29.0)	2 (11.1)	0.235
Above knee	12 (14.8)	13 (21)	2 (11.1)	0.492
Bellow knee	2 (2.5)	1 (1.6)	0	0.769
Minor Amputation	3 (3.7)	5 (8.1)	0	0.290
In hospital Mortality, n (%)	16 (19.8)	5 (8.1)	0	0.026

CV – Cardiovascular; PVD – Polyvascular Disease;

Figure 1 Legend – Study`s population selection Flow Diagram

Figure 2- Survival curves of Multivessel disease models for long-term results

1.A. Survival curves for Cardiovascular Mortality; 1.B Survival curves for Non-Cardiovascular Mortality; Figure 1.C Survival curves for All-cause Mortality.

STROCSS 2024 Guidelines			
Topic	**Item**	**Item Description**	**Page Number**
Title	**1**	**<u>Title</u>** - The word 'cohort' or 'cross-sectional' or 'case-control' is included* - Temporal design of study is stated (e.g. retrospective or prospective) - The focus of the study is clearly stated (e.g. population, setting, disease, exposure/intervention, outcome etc.) **STROCSS 2024 guidelines apply to all observational studies (e.g. cohort, cross-sectional, case-control etc.)*	3
Highlights	**2**	**<u>Highlights</u>** - Include three to five bullet points that summarise the key findings of the study - Provide a brief background to the study, the key results and clinical relevance	6
Abstract	**3a**	**<u>Structure</u>** - Provide a structured abstract that includes the following headings: 1. Background 2. Methods 3. Results 4. Conclusions	6
	3b	**<u>Background</u>** Briefly describe: - Relevant context - Scientific rationale for this study - Aims and objectives	6
	3c	**<u>Methods</u>** Briefly describe: - Type of study design (e.g. cohort, case-control, cross-sectional etc.) - Specification of study design (e.g. retro-/prospective, single/multi-centred etc.) - All patient groups involved, including control group, if applicable - Exposure/interventions (e.g. type, operators, recipients, dates and time frames etc.) - Outcome measures - explicitly state primary and secondary outcome(s), where appropriate - Statistical methods of assessment used, where applicable	6
	3d	**<u>Results</u>** Briefly describe: - Summary data - Principal findings with qualitative descriptions - Statistical findings and their significance, where appropriate	6

	3e	**<u>Conclusion</u>** - Describe key conclusions briefly - Refer to implications for clinical practice and public health - Describe the need for and direction of future research - Include a concise statement that encapsulates the significance of the research and its contribution to the field	6
Keywords	**4**	**<u>Keywords</u>** - Include three to six keywords that identify what is covered in the study (e.g. patient population, diagnosis, or surgical intervention) - Include study type as a keyword (e.g. cohort study, cross-sectional study, case-control study etc.) - Include surgical speciality as one of the keywords. - Include study location as one of the keywords.	4
Introduction	**5a**	**<u>Introduction</u>** By referencing key literature throughout, comprehensively describe: - Relevant background and scientific rationale for study - Aims and objectives - Research question and hypotheses, where appropriate - Potential impact of research on future clinical practice - Economic relevance of study to society	7-8
	5b	**<u>Guideline citation</u>** - At the end of the introduction, refer to the STROCSS 2024 publication by stating: 'This cohort/cross-sectional/case-control study has been reported in line with the STROCSS guidelines [*include citation*]'	9
Methods: **Study Design**	**6a**	**<u>Study design</u>** - State the type of study design (e.g. cohort, cross-sectional, case-control etc.) - Describe other key elements of study design (e.g. retro-/prospective, single/multi-centred etc.) - Specify the duration of the study, including start and end dates	8-9
	6b	**<u>Setting and timeframe of research</u>** Comprehensively describe: - Specific geographical location - Nature of institution (e.g. primary/secondary/tertiary care setting, district general hospital/teaching hospital, public/private, low-resource setting etc.) - Timeline for study, including dates for recruitment, exposure, follow-up, data collection etc. - Any deviations from the initial study design plan	8

		or changes to the timeline during the research, with reasons and implications stated	
	6c	**<u>Study groups</u>** - Total number of participants - Number of groups - Number of participants in each group - Detail exposure/intervention allocated to each group - Inclusion and exclusion criteria with clear definitions	8
	6d	**<u>Subgroup analysis</u>** Comprehensively describe: - How subgroups were defined - Planned subgroup analyses - Methods used to examine subgroups and their interactions	8
	6e	**<u>Follow up</u>** If applicable, comprehensively describe: - Time, length, frequency, location and methods of follow-up (e.g. mail, telephone, with whom etc.) - Any specific long-term surveillance requirements (e.g. imaging surveillance of endovascular aneurysm repair) - Any specific post-operative instructions (e.g. post-operative medications, targeted physiotherapy etc.)	8
Methods: Participant Recruitment	**7a**	**<u>Recruitment</u>** Comprehensively describe: - Period of recruitment - Methods of recruitment to each patient group (e.g. all at once, in batches, continuously till desired sample size is reached etc.) - Sources of recruitment (e.g. physician referral, study website, social media, posters etc.) - Any monetary/non-monetary incentivisation of participants to encourage involvement should be declared *(the nature of any incentives provided must be clarified)* - Any challenges encountered during the recruitment processes, including how they were addressed	8
	7b	**<u>Sample size</u>** Comprehensively describe: - Analysis to determine optimal sample size for study accounting for population/effect size - Power calculations with justifications for chosen statistical power, where appropriate - Margin of error calculation - Any associated ethical considerations	11
Methods: Intervention and Outcomes	**8a**	**<u>Pre-intervention considerations</u>** Comprehensively describe any preoperative patient optimisation: - Lifestyle optimization (e.g. weight loss, smoking	

		cessation, glycaemic control etc.) - Medical optimisation (e.g. medication review, treating hypothermia/-volemia/-tension, ICU care etc.) - Procedural optimisation (e.g. nil by mouth, enema etc.) - Other (e.g. psychological support, physiotherapy etc.)	8
	8b	**<u>Intervention</u>** Comprehensively describe: - Type of intervention and reasoning (e.g. pharmacological, surgical, physiotherapy, psychological etc.) - Aim of intervention (e.g. preventative/therapeutic) - Total cost of performing the intervention - Degree of novelty of intervention - Any learning required for intervention - Prevalence or frequency at which the intervention is performed - Concurrent treatments (e.g. antibiotics, analgesia, antiemetics, VTE prophylaxis etc.) - Manufacturer and model details, where appropriate	9-10
	8c	**<u>Intra-intervention considerations</u>** Using figures and other media to illustrate wherever appropriate, comprehensively describe: - Details pertaining to administration of intervention (e.g. anaesthetic, positioning, location, preparation, equipment needed, devices, sutures, operative techniques, operative time etc.) - For pharmacological therapies, the formulation, dosages, routes, strength and durations - For surgery, any post-operative instruction (e.g. when to remove staples or sutures) - The degree of novelty for a surgical technique/device (e.g. 'first in human')	10
	8d	**<u>Operator details</u>** Comprehensively describe: - Requirement for additional training - Learning curve for technique, including how it was evaluated (e.g. number of cases required to reach a defined level of proficiency) - Relevant training, specialisation and operator's experience (e.g. average number of the relevant procedures performed annually) - Any institutional support that was provided to operators to facilitate their training	9-10
	8e	**<u>Setting of intervention</u>** Comprehensively describe: - Setting in which the intervention was performed - Level of experience the centre has in performing the intervention	9
	8f	**<u>Quality control</u>** Comprehensively describe:	

		- Measures taken to reduce inter-operator variability (e.g. regular team meetings, calibration exercises) - Measures taken to ensure consistency in other aspects of intervention delivery (e.g. data collection) - Measures taken to ensure quality in intervention delivery	8
	8g	**<u>Post-intervention considerations</u>** Comprehensively describe: - Post-operative instructions and care (e.g. avoid heavy lifting, dietary restrictions etc.) - Follow-up measures - Future surveillance requirements (e.g. blood tests, imaging etc.) - How patient engagement with post-intervention instructions will be encouraged and monitored - If applicable, the criteria for patient discharge from the medical facility	10
	8h	**<u>Definition of outcomes</u>** - Define primary outcomes, including validation with full reference to relevant studies, where applicable - Define secondary outcomes, where appropriate - Describe methods or instruments used to measure each outcome, with full reference given if validated - Describe follow-up period for outcome assessment, divided by group	11
	8i	**<u>Statistics</u>** Comprehensively describe: - Statistical tests and statistical package(s)/software used - Rationale behind the statistical tests/software of choice - Confounders and their control, if known - Analysis approach (e.g. intention to treat/per protocol) - Any subgroup analyses - Level of statistical significance - How the results of the statistical analyses are presented (e.g. p-values, confidence intervals, point estimates etc.)	11
Results	**9a**	**<u>Participants</u>** Comprehensively describe: - With reasons, the flow of participants (recruitment, non-participation, cross-over and withdrawal), using a figure to illustrate where appropriate - Population demographics (e.g. age, gender, relevant socio-economic features, prognostic features etc.) - Any significant numerical differences across groups - If applicable, the longitudinal changes in	12-13

		participant flow/demographics over time	
	9b	**<u>Participant comparison</u>** - Include table comparing baseline characteristics of cohort groups, with statistical data included - In a concise manner, highlight the principal, significant findings - Describe any group matching, with methods	12-13
	9c	**<u>Outcomes</u>** Comprehensively describe: - Clinician-assessed and patient-reported outcomes (e.g. questionnaires with quality-of-life scales) for each group - Expected versus attained outcomes, as assessed by the clinician* - Primary and secondary outcomes, as previously defined (8i) - Details of when the outcomes were recorded (e.g. at how many months/years post-operatively) - Relevant photographs and imaging are desirable - Any confounding factors and state which ones are adjusted and how - Any changes to interventions, with rationale and diagram, if appropriate **NB: reference relevant literature to inform expected outcomes*	12-13
	9d	**<u>Tolerance</u>** Comprehensively describe: - Assessment of tolerability of exposure/intervention within patient groups - Methods of measuring tolerance/adherence - If applicable, specific patient perspectives - Whether these results will have an impact on the long-term applicability of the findings in clinical practice - Loss to follow-up (fraction and percentage), with reasons	12-13
	9e	**<u>Complications</u>** Comprehensively describe: - Adverse events, and classify according to Clavien-Dindo classification* - Timing of adverse events - Precautionary measures taken to prevent complications (e.g. antibiotic or venous thromboembolism prophylaxis) - Management of adverse events (e.g. blood transfusion, wound care, revision surgery etc.) - If applicable, whether the complication was reported to the national agency/pharmaceutical company - If applicable, specify whether any complications were discussed locally and the impact of such discussions (e.g. during team morbidity & mortality meetings) - State explicitly if there were no	12-13

		complications/adverse outcomes **Dindo D, Demartines N, Clavien P-A. Classification of Surgical Complications. A New Proposal with Evaluation in a Cohort of 6336 Patients and Results of a Survey. Ann Surg. 2002; 240(2): 205-213*	
	9f	**<u>Key results</u>** Describe: - Key findings, supported by relevant raw data and corresponding statistical analyses with significance	12-13
Discussion	**10a**	**<u>Principal findings</u>** By referencing key, relevant literature throughout, comprehensively describe: - Summary of key findings and conclusions - Rationale behind conclusions drawn - Comparison to current gold standard of care, current guidelines or similar research - Implications of findings for future clinical practice and guidelines - Relevant hypothesis generation	13-16
	10b	**<u>Strengths and limitations</u>** Comprehensively describe: - Strengths of the study - Weaknesses and limitations of the study - Measures taken to overcome the limitations, if applicable - Potential impact on results and their interpretation - Assessment and management of bias - Deviations from protocol, with reasons stated	16-17
	10c	**<u>Relevance and implications</u>** Comprehensively describe: - Relevance of findings - Potential implications for future clinical practice and guidelines - Measures that can be taken to enhance the quality of research study - Need for and direction of future research	17
Conclusion	**11**	**<u>Conclusions</u>** - Summarise key conclusions, in a concise and succinct manner - Outline scope for and direction of future research	17-18
Additional information	**12a**	**<u>Registration</u>** - In accordance with the Declaration of Helsinki*, state the unique research registration number and where it was registered, with a hyperlink to the registry entry *(this can be obtained from ResearchRegistry.com, ClinicalTrials.gov, ISRCTN etc.)* - *N.B. All retrospective studies should be registered before submission; it should be stated that the research was retrospectively registered.*	9

		******'Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject'*	
	12b	**<u>Ethical approval</u>** - Whether ethical approval was needed or not, stated explicitly - Reason(s) why ethical approval was/was not needed - Name of the body giving ethical approval and approval number	9
	12c	**<u>Informed consent</u>** - State explicitly whether informed consent was obtained, or not. - State reason(s) why informed consent was/was not obtained - State the nature of consent (e.g. verbal, written, digital/virtual)* - The authors must provide evidence of consent, where applicable, and if requested by the journal - Consent should be provided for both the original intervention/procedure and publication of the study *If consent was not provided by the patient themselves, explain why (e.g. death of the patient and consent provided by next of kin). If the patient or family members were untraceable, then document the tracing efforts undertaken	8
	12d	**<u>Protocol</u>** - Give details of protocol (a *priori* or otherwise) including how to access it (e.g. web address, DOI etc.) - Give details of protocol registration (e.g. protocol registration number, protocol registry's name etc.) - If published in a journal, cite and provide a full reference - If applicable, detail any amendments made to the original protocol, giving reasons why the changes were made	21
Declarations	**13a**	**<u>Contributorship</u>** - Acknowledge any patient and/or public and/or professional involvement in research - Report the extent of involvement of each contributor, specifically stating what they contributed to (e.g. patient recruitment, defining research outcomes, dissemination of results etc.).	NA
	13b	**<u>Conflicts of interest</u>** - Conflicts of interest, if any, are described	18
	13c	**<u>Funding</u>** - Sources of funding (e.g. grant details), if any, are clearly stated - Role of funder stated - Guarantor named	18

	13d	**<u>Data sharing statement</u>** - Explicitly state whether or not the datasets generated during study are available on request	NA

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