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FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2020/2021

Francisca Vieira da Silva Caldeira de Albuquerque

Red blood cell distribution width predicts myocardial infarction and mortality after vascular surgery – A prospective cohort study

A amplitude de distribuição dos glóbulos rubros prediz a ocorrência de enfarte do miocárdio e morte após cirurgia vascular – Estudo coorte prospetivo

Abril, 2021

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Mestrado Integrado em Medicina

Área: Cirurgia Vascular

Tipologia: Dissertação

Trabalho efetuado sob a Orientação de:

Professora Doutora Marina Felicidade Dias Neto

E sob a Coorientação de:

Dr. João Manuel Palmeira da Rocha Neves

Trabalho organizado de acordo com as normas da revista:

Surgery

Abril, 2021

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UC Dissertação/Projeto (6º Ano) - DECLARAÇÃO DE INTEGRIDADE

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DESIGNAÇÃO DA ÁREA DO PROJECTO

Cirurgia Vascular

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

Red blood cell distribution width predicts myocardial infarction and mortality after vascular surgery - A prospective cohort study

ORIENTADOR

Marina Felicidade Dias Neto

COORIENTADOR (se aplicável)

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É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☒
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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, 08 / 04 / 2021

Assinatura conforme cartão de identificação: Francisca Albuquerque

Title

Red blood cell distribution width predicts myocardial infarction and mortality after vascular surgery - A prospective cohort study

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Abstract

Background: Hematological parameters, such as the red blood cell distribution width-coefficient variation (RDW-CV) and red blood cell distribution width-standard deviation (RDW-SD), have been shown to be strongly associated with postoperative cardiovascular events and all-cause mortality. This study aims to investigate the association between preoperative hematological parameters and postoperative outcomes, including myocardial infarction (MI) and all-cause mortality.

Methods: All adult consecutive patients submitted to elective arterial vascular surgery from January to April 2015 at a university hospital were included in this prospective observational cohort study. The primary outcome was 30-day all-cause mortality. The secondary outcome was 30-day MI.

Results: In the univariate analysis of mortality, the prevalence of atrial fibrillation, chronic kidney disease (CKD) and dependent functional status was higher in deceased patients. After multivariable analysis, age (adjusted OR 1.08, 95%CI 1.01-1.15, p=0.027) and RDW-SD (adjusted OR 1.08, 95%CI 1.01-1.16, p=0.032) remained independent predictors of mortality. In the univariate analysis of MI, the prevalence of Diabetes, CKD, dependent functional status, ASA physical status IV and insulin medication was significantly higher in patients with postoperative MI. After multivariable analysis, dependent functional status (adjusted OR 4.8, 95%CI 1.6-15.0, p=0.007), insulin medication (adjusted OR 4.4, 95%CI 1.5-12.6, p=0.007) and RDW-SD (adjusted OR 1.10, 95%CI 1.02-1.19, p=0.020) were independent predictors of MI.

Conclusion: RDW may play an important role in the perioperative evaluation of patients submitted to vascular surgery. RDW-SD independently predicts postoperative MI and mortality, and as such, it may provide valuable information for the prevention and early management of adverse cardiovascular outcomes.

Keywords

Red blood cell distribution width (RDW), Neutrophil-lymphocyte ratio (NLR), Prognosis, Myocardial Infarction, Mortality

Introduction

Cardiovascular diseases are a leading cause of morbidity and mortality worldwide [1]. The identification and strict control of cardiovascular risk factors, such as hypertension, diabetes, obesity, smoking, or dyslipidemia, play an important role in the prevention of future cardiovascular events [2], however, there are other useful markers that may provide valuable information for the risk stratification and early management of these events. The red blood cell distribution width (RDW) is a measure of the variability in size of circulating erythrocytes [3-5]. It measures the difference in size between the largest and the smallest cells, reflecting the heterogeneity amongst these cells' dimensions. In most automated laboratory blood counters it is expressed as a coefficient of variation (RDW-CV), defined by the ratio between RDW standard deviation (RDW-SD) and the mean corpuscular volume [6, 7]. The term anisocytosis corresponds to an increase in the RDW, meaning that the size distribution of red blood cells has a greater variation when compared to normal RDW values. Traditionally, this blood count parameter has been exhaustively studied in hematological diseases, such as bone marrow dysfunction or anemia due to deficiencies in vitamin B12, folate or iron [7]. Nowadays, new evidence supports a correlation between the RDW and the development of adverse cardiovascular events, such as myocardial infarction (MI), stroke, coronary disease, heart failure, or peripheral artery disease (PAD) [4, 6, 8]. Recent studies show that high RDW values are associated with all-cause mortality both in patients with and without known cardiac disease, as well as a greater mortality rate in older individuals in the presence or absence of major age-associated diseases [4]. Moreover, some reveal that the RDW baseline value is a strong and independent predictor of poor prognostic outcomes following cardiovascular interventions, such as percutaneous coronary intervention [4, 9], carotid endarterectomy [8], or percutaneous transluminal angioplasty [9].

The neutrophil-lymphocyte ratio (NLR) is another parameter that is easily accessible in a complete blood count. Recent studies have demonstrated that NLR is related with the severity and long-term prognosis of cardiovascular diseases, as in acute coronary syndrome, heart failure, or valvular heart disease [1]. It is considered an indicator to assess systemic inflammation, and has been used in some studies to predict episodes of stenosis secondary to inflammation, such as ischemic heart disease [10].

Despite the evolution of anesthetic and surgical techniques in vascular surgery, along with improved perioperative planning and monitoring, postoperative mortality is still significant [11, 12]. Patients who are proposed to vascular surgery usually have multiple cardiovascular risk factors that increase the risk of major adverse cardiovascular events [13]. Previous studies have reported independent risk factors for postoperative mortality, including age, PAD, smoking status, chronic kidney disease (CKD), atrial fibrillation, and leucocyte count [11, 12]. Myocardial infarction following vascular surgery may range from 0.3% to 36% [13]. Ischemic heart disease, atrial fibrillation and insulin-treated diabetes mellitus have been identified as independent predictors of major adverse cardiac events, including MI [13].

This study aims to evaluate the potential role of preoperative hematological parameters in predicting perioperative outcomes, including MI and all-cause mortality.

Methods

Study Design, Setting and Participants

A prospective observational cohort study was designed including all adult consecutive patients submitted to elective arterial vascular surgery from January to April 2015 at a university hospital. The protocol was approved by the institutional ethics committee (number CES 04-15). Patients' consent was obtained before inclusion. The protocol is registered in ClinicalTrials.gov with the identifier NCT04051749. This manuscript is reported according to Strengthening the Reporting of Cohort Studies in Surgery (The STROCSS Statement) [14] and Strengthening the Reporting of Observational Studies in Epidemiology (The STROBE Statement).[15]

Data collection

Patients were all evaluated by a vascular surgeon and an anesthesiologist before the surgery. Variables were prospectively collected before and during surgery: age, gender, medical history, usual medication, vital signs, laboratory results, electrocardiographic findings, American Society of Anesthesiology (ASA) physical status, type and duration of surgery/anesthesia, drug administration, estimated blood loss and transfusion requirements. Preoperative cardiac evaluation was based on symptoms, medical history, functional capacity, dyspnea/orthopnea, and usual medication. Patients with coronary artery disease or heart failure were only included in the study if their health condition was deemed as stable. Recent ischemic pain, greater intensity/longer duration than usual, caused by less effort or occurring at rest were referred to the Cardiology Department, and additional studies (echocardiography, cardiac stress test, coronary angiography, or cardiac magnetic resonance) or laboratory analysis (Brain Natriuretic Peptide, troponins, arterial blood gas) were requested as necessary. Surgeries were divided into intermediate

or high-risk surgery according to the joint guidelines of European Society of Cardiology (ESC) and European Society of Anesthesiology (ESA) [16].

Outcomes

Postoperative assessment was performed during the hospital stay and in the outpatient clinic. The primary outcome was 30-day all-cause mortality. The secondary outcome was 30-day MI, defined as chest pain, electrocardiographic ST segment variations or a rise in high sensitivity myocardial Troponin levels superior to 34 ng/L, following the ESC/American College of Cardiology criteria [17]. Information regarding other major cardiovascular events (*de novo* atrial fibrillation or heart failure including pulmonary edema, ventricular fibrillation, cardiac arrest or complete heart block) was also recorded.

Statistical analysis

Comparisons in univariate analysis were performed using Qui square or Fisher's tests for categorical and for continuous selected parametric (independent samples t-test) or non-parametric (Mann-Whitney-U) tests accordingly. Descriptive statistics summarized the data. Variables with $p<0.05$ in the univariate analysis were included in the multivariate logistic regression to determine the independent predictors, calculating the Odds Ratio (OR) and its 95% confidence interval (CI). Hemoglobin levels were included in the multivariable models to exclude RDW variation due to anemia. We analyzed the Area Under Receiver Operating Characteristics Curve (AUROC) of the different laboratory results and the multivariable analysis by the forward model to measure their predictive discrimination power. The Hosmer-Lemeshow test was used to determine the goodness of fit of our model (calibration), $p>0.05$ for no significant difference between the

predictive model and observed data. Stata 14 and SPSS (IBM Corp., version 26.0, Armonk, NY, USA) were used for data analysis.

Results

In this prospective cohort, 297 patients were submitted to a Vascular Surgery and included in the study. Table 1 shows the main features of the surgical interventions to which they were submitted. Forty three percent (127 out of 297) were high risk surgery according to ESC/ESA guidelines. Table 2 shows the univariate analysis of mortality (primary outcome). The prevalence of atrial fibrillation, CKD and dependent functional status in activities of daily living was higher in patients who died. These patients were more likely medicated with diuretics and less with statins. The values of RDW and urea were significantly higher in deceased patients.

The univariate analysis of MI (secondary outcome), as shown in Table 3, reveals that patients with MI had longer hospital stay (44 vs 14 days, p=0.002) and higher mortality (20 vs 5%, p=0.005) corresponding to an OR of 6.4, 95%CI (1.5-26.2), p=0.011. The prevalence of Diabetes, CKD, dependent functional status, ASA physical status IV and insulin medication was higher in patients who had postoperative MI. The values of RDW-SD, NLR and serum creatinine were significantly higher in patients with MI. Patients with a NLR greater than 2.9 had more MI events: 9.5 vs 3.4%, p=0.033.

After multivariable logistic regression analysis, age and RDW-SD remained independent predictors of mortality (Table 4). The increase in risk is 8% per year (adjusted OR 1.08, 95%CI 1.01-1.15, p=0.027) and 8% per unit increase in RDW-SD (adjusted OR 1.08, 95%CI 1.01-1.16, p=0.032). The AUROC to predict mortality was 0.81 (95%CI 0.71-0.91) for the RDW-SD alone and raised to 0.83 (95%CI 0.70-0.96) when combining age (Figure 1).

Table 5 presents the multivariable analysis of MI that resulted in three independent predictors: dependent functional status (adjusted OR 4.8, 95%CI 1.6-15.0, p=0.007),

insulin medication (adjusted OR 4.4, 95%CI 1.5-12.6, p=0.007) and RDW-SD (adjusted OR 1.10, 95%CI 1.02-1.19, p=0.020). The increase in risk is 10% per unit of RDW-SD. The NLR was significant in the univariate analysis (OR 1.07, p=0.048) but was not an independent predictor of MI in the multivariable analysis. The AUROC to predict MI was 0.66 (95%CI 0.50-0.80) for the RDW-SD, 0.71 (95%CI 0.59-0.84) for NLR and 0.79 (95%CI 0.69-0.90) when combining the three independent predictors (Figure 2).

Discussion

The results of this prospective observational cohort study demonstrate that an increase in the RDW-SD value is a significant independent predictor of all-cause mortality and MI in the early postoperative period after elective arterial vascular surgery. Also, an increase in the NLR has a reasonable predictive ability for MI events.

The present findings support previous evidence that these readily available hematological parameters exhibit a good predictive capacity for all-cause mortality and adverse cardiovascular events [1, 4, 6]. Despite the existence of several studies that prove the association between RDW or NLR and cardiovascular diseases, the present study has further evidenced that these parameters are significant predictors of adverse outcomes following vascular surgery.

The pathophysiological mechanisms that lead to the association between the RDW or NLR and adverse cardiovascular events are still not fully understood, however, there are some hypotheses that sustain this association. Prior studies have shown that there is a positive association between the RDW and inflammatory biomarkers, such as C-reactive protein (CRP), interleukin 6, erythrocyte sedimentation rate, soluble tumor necrosis factor, and oxidative stress [18, 19]. These play an important role in the inhibition of erythrocyte maturation at the bone marrow, which results in anisocytosis, suggesting that RDW reflects the inflammatory state required for the progression of atherosclerotic disease [2]. Moreover, some studies have demonstrated that inflammatory cytokines can suppress the synthesis of erythropoietin, causing a dysregulation in the red blood cells' maturation process [5]. Oxidative stress is strongly related with the erythrocytes' variability in size, since it shortens these cells' lifespan and impairs iron metabolism, leading to the production and release of immature forms into the systemic circulation [3, 5]. Additionally, elevated RDW values are associated with a decrease in erythrocyte deformability, which

in turn leads to a higher propensity for developing thrombotic events as well as an impaired blood flow, leading to tissue ischemia [20]. All these factors predispose the patient to a greater susceptibility for the emergence of adverse cardiovascular outcomes, resulting in a worse clinical prognosis. The NLR has been broadly studied as a marker of systemic inflammation and hence, of cardiovascular risk [2, 21]. It has been proven that neutrophils contribute to endothelial dysfunction along with the recruitment of monocytes to atherosclerotic lesions, leading to the disruption of atherosclerotic plaques [2]. This supports the impact that these cells have in the development of atherosclerotic disease, which in turn contributes to major adverse cardiovascular events.

In this study, atrial fibrillation (AF) was more prevalent in deceased patients. Previous studies suggest that inflammation and oxidative stress take part in the primary pathways that lead to cardiac arrhythmias [1]. AF has been proven to be a strong risk factor for cerebrovascular and cardiovascular mortality including in the postoperative period, as the main causes of death are stroke, ischemic heart disease, heart failure and myocardial infarction [22-24].

The prevalence of CKD was higher in both deceased patients and patients who had postoperative MI. CKD is intimately related to cardiovascular disease, probably due to the multiple risk factors which they have in common, including hypertension, diabetes mellitus, dyslipidemia, and advanced age [25]. Other risk factors, such as anemia, proteinuria, oxidative stress and inflammation, also take part in the development of these diseases, since they increase the risk of atherosclerosis and cardiac dysfunction, leading to ischemic disease and cardiomyopathy [25]. Evidence suggests that there is a direct correlation between the prevalence of cardiovascular disease and the severity of CKD [25]. This contributes to both major cardiovascular events, such as MI, and an increased risk for long-term mortality.

Dependent functional status was more prevalent in deceased patients and was an independent predictor of postoperative MI. Prior studies have proven that patients who are functionally dependent have a higher incidence of comorbid disease and exhibit more often malnutrition and cognitive dysfunction [26, 27]. Furthermore, evidence shows that these patients have a greater mortality rate when compared with functionally independent individuals [26, 27]. As such, preoperative dependent functional status could be used as an indicator of adverse outcomes following surgical interventions.

The prevalence of diabetes mellitus was greater in patients who had postoperative MI. Diabetes is associated with an increased risk of microvascular and macrovascular complications [19, 28]. Although not fully understood, there is evidence that hyperglycemia has a negative impact on the clotting mechanism, which can consequently increase the risk of thrombosis, especially at the coronary arteries [29]. Besides this, elevated blood glucose levels accelerate the development of atherosclerotic plaques, contributing to a higher risk of macrovascular complications, namely MI [29]. Furthermore, insulin-dependent diabetes was an independent predictor of postoperative MI. Previous studies have shown that insulin-treated diabetes is associated with a greater risk of developing major cardiovascular events, such as MI or stroke, when compared with no insulin medication [30]. Nevertheless, the role of insulin use in the risk of adverse cardiovascular outcomes is still not fully understood. It is uncertain whether it in fact increases the risk of adverse events or whether it represents advanced diabetic disease that leads to a greater predisposition for worse clinical prognosis [30]. Other studies have found a correlation between the metabolic effects of insulin therapy, namely hypoglycemia and weight gain, and greater cardiovascular risk [31]. Hypoglycemia, as a result of intensive insulin treatment, has been associated with life-threatening cardiovascular complications, such

252 as cardiac arrhythmias, with prolonged QT intervals and abnormal T wave morphology,
253 and myocardial ischemia [31].
254 This study focuses on short-term outcomes and a major limitation is the lack of longer
255 follow-up. Data on other factors that might influence the RDW, such as nutritional
256 deficiencies in folate or vitamin B12, or blood transfusions were not evaluated and
257 included in the database. Inclusion of patients may have selection bias since we only
258 included patients that were submitted to elective surgery and more fragile individuals are
259 less likely to be proposed to invasive procedures. This study was performed in a large
260 academic teaching institution, which might affect the external validity of the results to
261 community hospitals.

Conclusion

The use of hematological parameters as prognostic biomarkers has been widely investigated over the last years since these are inexpensive, routinely measured in clinical practice and easily accessible in all automatic complete blood counters. The results of this prospective cohort study suggest that the RDW may play an important role in the perioperative evaluation of patients submitted to elective arterial vascular surgery, and may provide valuable information for the prevention and early management of postoperative major adverse cardiovascular events and mortality.

Age and RDW-SD were identified as independent predictors of mortality, and dependent functional status, RDW-SD and insulin medication as independent predictors of MI. The RDW-SD was deemed as having a better predictive capacity than the RDW-CV for the outcomes mortality and MI.

COI / Disclosures

The authors have no related conflicts of interest to declare.

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

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Table 1. List of elective procedures performed.

Lower extremity surgery	Femoro-popliteal bypass	28
	Femoro-distal bypass	6
	Endovascular therapy	44
	Major amputation	45
	Minor amputation	39
	Debridement	29
Aortoiliac revascularization	Open	19
	Endovascular	9
Aortoiliac aneurysm repair	Open	2
	Endovascular	8
Carotid endarterectomy		36
Hemodialysis access		24
Other		8
Total		297

Table 2. Demographics and morbidity of the patients by 30-day mortality.

Variables		Survival group (n=286)	Mortality group (n=11)	p value
Age (years), median [IQR]		65 [58-74]	77 [65-82]	**0.003**[a]
Male gender, n(%):		203 (71.0)	8 (72.7)	0.900[b]
Prior medical history, n(%):				
Arterial Hypertension		209 (73.1)	8 (72.7)	0.980[b]
Peripheral Arterial Disease		160 (56.1)	7 (63.6)	0.761[b]
Diabetes		154 (54.0)	3 (27.3)	0.122[b]
Current Smoker		125 (43.9)	6 (54.5)	0.546[b]
Chronic Kidney Disease		90 (31.6)	7 (63.6)	**0.026**[b]
Cerebrovascular Disease		60 (21.1)	1 (9.1)	0.470[b]
Coronary Disease		59 (20.7)	4 (36.4)	0.255[b]
Congestive Heart Failure		35 (12.3)	2 (18.2)	0.634[b]
Atrial fibrillation		15 (5.3)	3 (27.3)	**0.003**[b]
Dependent functional status, n(%)		24 (8.4)	3 (27.3)	**0.033**[b]
ASA physical status, n(%)	II/III	267 (93.6)	9 (81.8)	0.146[b]
	IV	19 (6.7)	2 (18.2)	
Usual medication, n(%):				
Antiplatelet drug		181 (63.5)	7 (63.6)	0.993[b]
Statin		183 (64.2)	3 (27.3)	**0.013**[b]
Diuretic		89 (31.2)	7 (63.6)	**0.024**[b]
Insulin		75 (26.3)	1 (9.1)	0.299[b]
Beta-Blocker		71 (24.9)	4 (36.4)	0.074[b]
Pre-op lab results, median [IQR]:				
Hemoglobin (g/dL)		11.9 [10.3-13.8]	11.3 [10.1-12.7]	0.456[a]
Serum Creatinine (mg/dL)		0.9 [0.7-1.5]	1.7 [0.9-3.0]	0.060[a]
Serum Urea (mg/dL)		42 [31-63]	78 [41-123]	**0.015**[a]
[Na^+] mEq/L		137 [135-140]	136 [133-139]	0.628[a]
[K^+] mEq/L		4.4 [4.0-4.8]	4.0 [3.5-4.5]	0.087[a]
[Cl^-] mEq/L		102 [99-105]	101 [97-107]	0.686[a]
Blood glucose (mg/dl)		113 [92-168]	96 [82-138]	0.252[a]
RDW-CV		14.0 [13.1-15.0]	15.5 [14.5-16.5]	**0.009**[a]
RDW-SD		45.0 [42.7-49.1]	50.9 [49.5-55.7]	**<0.001**[a]
NLR		2.8 [2.0-4.8]	4.7 [2.0-7.1]	0.241[a]
Postoperative MI, n(%)		16 (5.6)	3 (27.3)	**0.004**[b]

[a)] Mann-Whitney test, [b)] Fisher's-exact test. IQR: Interquartile range [P25-P75]. ASA: American Society of Anesthesiology. NLR: Neutrophil-Lymphocyte ratio. RDW: Red Cell Distribution Width – CV: Coefficient of variation; SD: Standard deviation. MI: Myocardial Infarction

Table 3. Demographics and morbidity of the patients by 30-day Myocardial Infarction (MI).

Variables		Without MI (n=278)	With MI (n=19)	p value
Age (years), median [IQR]		65 [58-74]	66 [65-77]	0.135[a]
Male gender, n(%):		197 (70.9)	14 (73.7)	0.793[b]
Prior medical history, n(%):				
Arterial Hypertension		202 (72.7)	15 (78.9)	0.815[c]
Peripheral arterial disease		155 (56.0)	12 (63.2)	0.540[b]
Diabetes		142 (51.3)	15 (78.9)	**0.019**[c]
Current Smoker		120 (43.3)	11 (57.9)	0.216[b]
Chronic kidney disease		87 (31.4)	10 (52.6)	**0.034**[b]
Coronary artery disease		56 (20.2)	7 (36.8)	0.087[b]
Cerebrovascular disease		54 (19.5)	7 (36.8)	0.071[b]
Congestive heart failure		32 (11.9)	5 (30.0)	0.072[c]
Atrial fibrillation		15 (5.4)	3 (15.8)	0.099[c]
Dependent functional status, n(%)		19 (6.9)	8 (42.1)	**<0.001**[b]
ASA physical status, n(%)	II/III	259 (93.8)	15 (78.9)	**0.009**[c]
	IV	17 (6.2)	4 (21.1)	
Usual medication, n(%):				
Antiplatelet		172 (62.1)	16 (84.2)	0.082[c]
Statin		173 (62.5)	13 (68.4)	0.603[b]
Diuretic		87 (31.4)	9 (47.4)	0.151[b]
Beta-Blocker		71 (25.6)	4 (21.1)	0.790[c]
Insulin		64 (23.1)	12 (63.2)	**<0.001**[b]
Pre-op lab results, median [IQR]:				
Hemoglobin (g/dL)		11.9 [10.3-13.8]	11.5 [9.8-12.6]	0.233[a]
Serum Creatinine (mg/dL)		0.92 [0.68-1.48]	1.49 [0.84-3.47]	**0.010**[a]
Serum Urea (mg/dL)		42 [31-63]	58 [35-76]	0.090[a]
[Na^+] mEq/L		137 [135-139]	137 [134-141]	0.932[a]
[K^+] mEq/L		4.4 [4.0-4.8]	4.2 [3.6-4.7]	0.250[a]
[Cl^-] mEq/L		102 [99-105]	100 [97-106]	0.487[a]
Blood glucose (mg/dl)		111 [92-164]	89 [59-208]	0.675[a]
RDW-CV		14 [13.1-15.0]	14.8 [13.2-15.9]	0.134[a]
RDW-SD		45.0 [42.8-49.1]	50.2 [43.1-55.7]	**0.028**[a]
NLR		2.8 [2.0-4.6]	5.4 [2.8-8.5]	**0.002**[a]

Postoperative mortality, n(%)	14 (4.9)	5 (20.0)	**0.005[b]**
Length of stay (days), [IQR]	16 [6-37]	44 [24-68]	**0.002[a]**

[a)] Mann-Whitney test, [b)] Chi-square test, [c)] Fisher's-exact test. IQR: Interquartile range [P25-P75]. ASA: American Society of Anesthesiologists. NLR: Neutrophil-Lymphocyte ratio. RDW: Red Cell Distribution Width – CV: Coefficient of variation; SD: Standard deviation

Table 4. Multivariable analysis of 30-day mortality.

Variables	OR (95% CI)	p value	aOR (95% CI)	p value
Age	1.10 (1.03-1.17)	0.005	1.08 (1.01-1.15)	0.027
Chronic Kidney Disease	3.8 (1.1-13.3)	0.037		
Atrial Fibrillation	6.8 (1.6-28.1)	0.009		
Statin	0.2 (0.1-0.8)	0.023		
Diuretic	3.8 (1.1-13.5)	0.035		
RDW-CV	1.27 (1.02-1.59)	0.036		
RDW-SD	1.09 (1.02-1.16)	0.011	1.08 (1.01-1.16)	0.032

OR: Odds Ratio. CI: Confidence Interval. aOR: Adjusted Odds Ratio. RDW: Red Cell Distribution Width. CV: Coefficient Variation. SD: Standard Deviation.

Table 5. Multivariable analysis of 30-day Myocardial Infarction (MI).

Variables	OR (95% CI)	p value	aOR (95% CI)	p value
Diabetes	3.6 (1.2-11.0)	0.027		
Dependent status	9.9 (3.6-27.5)	<0.001	4.8 (1.6-15.0)	0.007
Insulin dependent	5.7 (2.2-15.1)	<0.001	4.4 (1.5-12.6)	0.007
NLR	1.07 (1.0-1.15)	0.048		
RDW-CV	1.30 (1.07-1.58)	0.009		
RDW-SD	1.11 (1.04-1.18)	0.002	1.10 (1.02-1.19)	0.020

OR: Odds Ratio. CI: Confidence Interval. aOR: Adjusted Odds Ratio. RDW: Red Cell Distribution Width. NLR: Neutrophil-Lymphocyte ratio. CV: Coefficient Variation. SD: Standard Deviation.

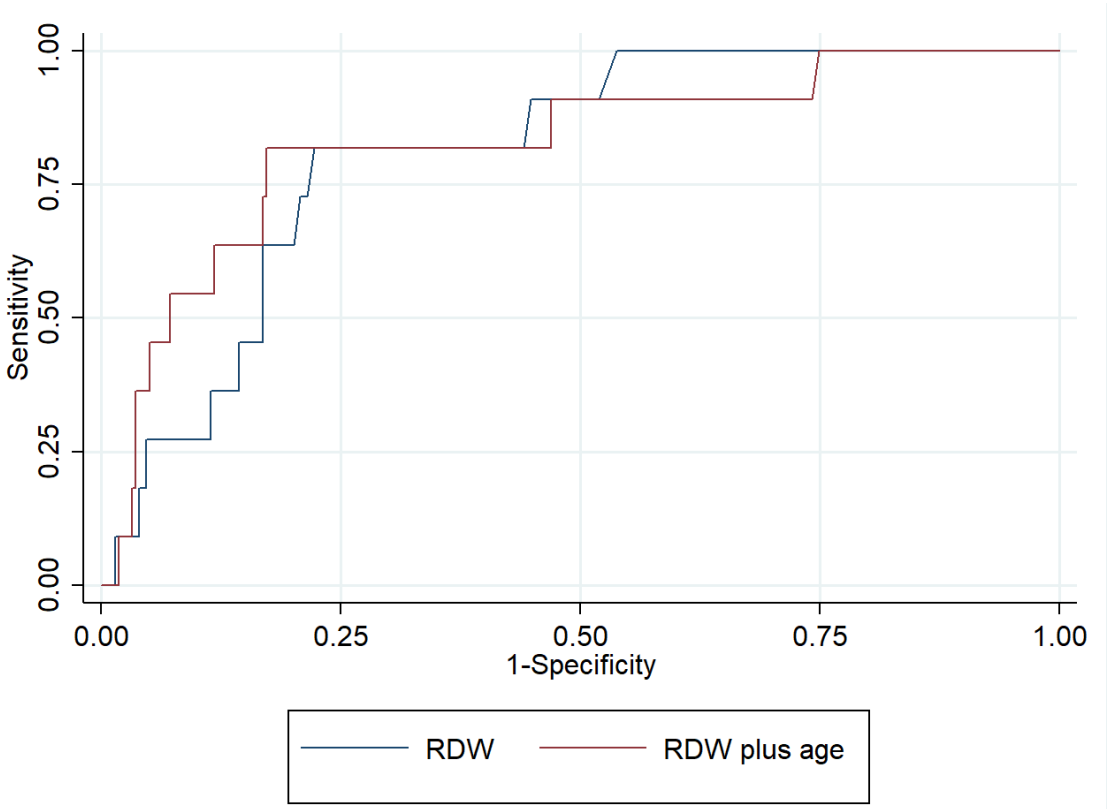

Figure 1. AUROC for 30-day Mortality.

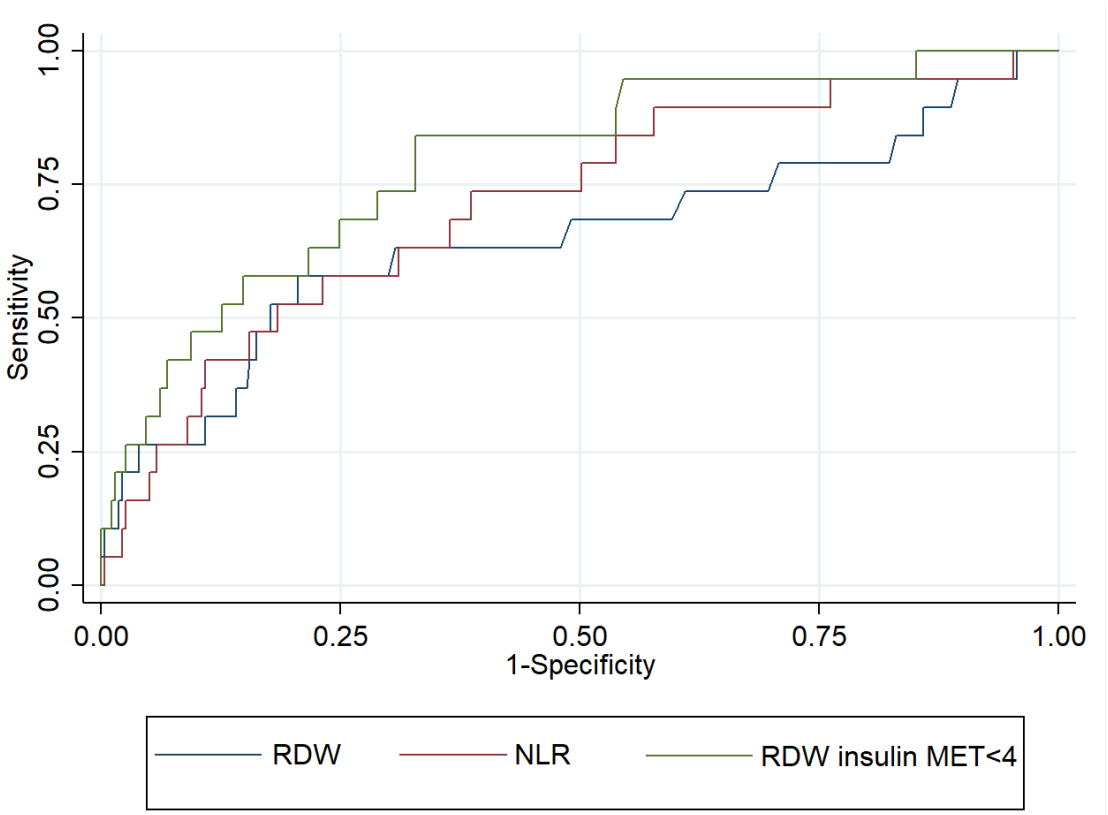

Figure 2. AUROC for 30-day Myocardial Infarction (MI).

Direcção Clínica
26/2/15 CES 04-15

AUTORIZADO
CONSELHO DE ADMINISTRAÇÃO @ REUNIÃO DE 05 MAR 2015
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Exmo. Senhor
Presidente do Conselho de Administração do
Centro Hospitalar de S. João – EPE

Assunto: Pedido de autorização para realização de estudo/projecto de investigação

Nome do Investigador Principal: Pedro José Vinhais Domingues Videira Reis

Título do projecto de investigação: *Scores* de estratificação e fatores de risco de *outcomes* adversos em cirurgia vascular

Pretendendo realizar no(s) Serviço(s) de Anestesiologia e Cirurgia Vascular do Centro Hospitalar de S. João – EPE o estudo/projecto de investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efectivação.
Para o efeito, anexa toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de S. João respeitante a estudos/projectos de investigação, à qual endereçou pedido de apreciação e parecer.

Com os melhores cumprimentos.

Porto, 22 / Dezembro / 2014

22/12/2014

O INVESTIGADOR/PROMOTOR

Pedro José V. Domingues Videira Reis

7. SEGURO

a. *Este estudo/projecto de investigação prevê intervenção clínica que implique a existência de um seguro para os participantes?*

SIM ☐ (Se sim, junte, por favor, cópia da Apólice de Seguro respectiva)
NÃO ☒
NÃO APLICÁVEL ☐

8. TERMO DE RESPONSABILIDADE

Eu, Pedro José Vinhais Domingues Videira Reis,
abaixo-assinado, na qualidade de Investigador Principal, declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (com as emendas de Tóquio 1975, Veneza 1983, Hong-Kong 1989, Somerset West 1996 e Edimburgo 2000) e da Organização Mundial da Saúde, no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo no decurso do actual internamento ou da mesma consulta.

Porto, 22 / Dezembro / 2014

Pedro José V. Domingues Videira Reis
O Investigador Principal

PARECER DA COMISSÃO DE ÉTICA PARA A SAÚDE DO CENTRO HOSPITALAR DE S. JOÃO

emitido na reunião plenária da CES de 27 / Janeiro / 2015

A Comissão de Ética para a Saúde APROVA por unanimidade o parecer do Relator, pelo que nada tem a opor à realização deste projecto de investigação.

Prof. Doutor Filipe Almeida
Presidente da Comissão de Ética

Comissão de Ética para a Saúde do HSJ

Parecer

Projecto de investigação: "*Scores* de estratificação e fatores de risco de *outcomes* adversos em cirurgia vascular".

Promotores:
- Não aplicável.

- Conceção e pertinência do estudo

- Trata-se de um estudo a realizar no âmbito de uma Tese de Doutoramento inserida no Programa Doutoral em Investigação Clínica e em Serviços de Saúde, na área da Anestesiologia e Medicina da dor, a defender na Faculdade de Medicina da Universidade do Porto (FMUP), que tem como objectivo principal realizar a medição da mortalidade e *outcomes* adversos após cirurgia vascular, a sua relação com fatores de risco pré e intra-operatórios e seu impacto no tempo de internamento e qualidade de vida.
- Tem ainda como outro objectivo a identificação de um *score* de estratificação de risco que seja simples, objetivo, preciso e com bom poder discriminativo que permita melhor prestação de cuidados e gestão de recursos.
- Será efectuada uma análise retrospectiva e prospectiva dos eventos adversos em doentes submetidos a cirurgia vascular arterial no Centro Hospitalar de S. João e assim realizado um estudo de associação entre as características do doente, factores intra-operatórios, parâmetros hemodinâmicos e analíticos no pós-operatório com mortalidade intra-hospitalar e aos 30 dias e complicações respiratórias, cardíacas, sépsis, incidência de reintervenção, tempo de internamento. Será efectuada ainda a análise da capacidade preditora de vários modelos de risco, todos eles pertinentes face aos objectivos do estudo.
- A análise retrospectiva dos eventos adversos será efectuada em doentes submetidos a cirurgia vascular entre janeiro de 2007 e julho de 2013 admitidos em Unidades de Cuidados Intensivos; a análise prospectiva de complicações pós-operatórias será realizada em doentes submetidos a cirurgia vascular arterial electiva no Centro Hospitalar de S. João EPE durante 6 meses consecutivos.
- Para tal será efetuada de forma anónima, consulta e análise dos dados do processo clínico.
- Os *outcomes* primários (mortalidade intra-hospitalar e aos 30 dias) e secundários (várias complicações, incidência de reintervenção, tempo de internamento em UCI e no hospital), estão todos bem explicitados e são pertinentes e adequados aos objectivos delineados para o estudo.
- Será realizado ainda um questionário sobre qualidade de vida aos 3 e 6 meses após cirurgia (medida com a versão portuguesa validade do EuroQoL 5 dimensões – EQ-5D)
- O estudo termina em dezembro de 2016 e não terá nem precisará de qualquer apoio financeiro.

- O protocolo de estudo, os critérios de inclusão e de exclusão estão suficientemente detalhados e não levantam quaisquer questões do foro ético.
- O Investigadora Principal, Dr. Pedro José Vinhais Domingues Videira Reis, interno de Anestesiologia do Centro Hospitalar de S. João EPE, (Orientador da Tese: Professor Fernando Abelha, docente da FMUP e Médico especialista de Anestesiologia do Centro Hospitalar de S. João EPE), dispõe das competências técnica e científica para a realização do estudo.
- O estudo será realizado nos Serviços de Anestesiologia, Cirurgia Vascular e Medicina Intensiva do Centro Hospitalar de S. João, EPE e dispõe da autorização para a sua realização pelos respectivos Diretores, Dra. Maria Fátima Pina, Dr. José Teixeira e Professor José Artur Paiva. Os serviços proponentes dispõem das condições necessárias para a realização do estudo.

– **Benefício/Risco**

- Dada a natureza do estudo e o facto de não haver qualquer intervenção suplementar ou procedimentos específicos para a realização do estudo (serão efectuados apenas os procedimentos médicos e cirúrgicos habituais aos doentes que vão participar no estudo), não haverá benefícios, riscos ou incómodos acrescidos para os participantes.

– **Respeito pela liberdade e autonomia do sujeito do ensaio**

- A folha de informação submetida à CES contém informação relevante numa linguagem acessível e relacionada com o tipo de estudo proposto.
- A gratuitidade do sujeito do ensaio em participar no estudo é igualmente garantida.
- Estão consignados os direitos e referenciadas as (não) consequências para o sujeito do estudo em não participar e, uma vez dado o seu consentimento, ter a possibilidade de exercer o direito de não continuar no estudo sem que daí resulte qualquer modificação dos cuidados médicos a prestar.

– **Confidencialidade dos dados**

- A confidencialidade e a privacidade dos dados são garantidas.

– **Indemnização por danos**

Não aplicável.

– **Continuação do tratamento**

Não aplicável.

- **Propriedade dos dados**

Do promotor.

Conclusão

Em face da análise do protocolo de "*Scores* de estratificação e fatores de risco de *outcomes* adversos em cirurgia vascular", proponho a sua aprovação pela CES do HSJ/FMUP.

Porto, 26 de janeiro de 2015

O Relator

Prof. Manuel Vaz Silva

SURGERY

Official journal of the Society of University Surgeons, Central Surgical Association, and the American Association of Endocrine Surgeons

AUTHOR INFORMATION PACK

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For 66 years, *Surgery* has published practical, authoritative information about procedures, clinical advances, and major trends shaping **general surgery**. Each issue features original scientific contributions and clinical reports. Peer-reviewed articles cover topics in **oncology**, **trauma**, **gastrointestinal**, **vascular**, and **transplantation surgery**. The journal also publishes papers from the meetings of its sponsoring societies, the Society of University Surgeons, the Central Surgical Association, and the American Association of Endocrine Surgeons.

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Surgery publishes review papers that are solicited by the Editors-In-Chief or pre-approved by the Editors-In-Chief. Authors interested in writing a review manuscript should correspond with the Editors-In-Chief prior to submitting an unsolicited manuscript, which is rarely accepted. Systematic reviews and meta-analyses, which are well-executed and either relevant or timely, are considered through the regular submission process and without Editor-In-Chief pre-approval. These manuscripts must follow the outline suggested by PRISMA (http://www.prisma-statement.org). Only the most clinically impactful systematic reviews and meta-analyses will be reviewed and considered for publication. All review manuscripts are subject to rigorous peer review.

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All invited commentaries are solicited by the Editors-In-Chief. Unsolicited commentaries may be considered, but pre-approval by the Editors is strongly recommended. The invited commentaries should be concise (not to exceed 1000 words) and should express the personal opinion of the author. An invited commentary should have a maximum of five (5) references and no tables or figures. Invited commentaries are related to manuscripts published in *Surgery*, but may include timely subjects of interest including topics of social significance.

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The Editors-in-Chief may request the preparation and submission of a series of related articles of a maximum length of 1,000-1,500 words, including a maximum of 10 references. The invited author may enlist the support of additional co-authors to write the maximum of 3-5 invited commentaries. The topics, selected by the Editors-in-Chief will be about new cutting edge subjects, often with a technical or technological focus.

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For Images in Surgery submissions, a maximum of two images is allowed, the text should be less than 500 words with a maximum of three (3) references. Manuscripts must strictly adhere to these criteria and will only be considered if the criteria are met. Images in Surgery will be published online only. The text of manuscript should present the case as an unknown with the corresponding images crucial to attaining the correct diagnosis or management. The author should present four (4) potential options for the correct answer to the unknown diagnosis or management and clearly indicate the one best answer. The options for answers will be posted on the website where readers can enter their answer and see the correct response.

Debates and Dilemmas
Surgery welcomes discussion of controversial topics or subject matter that warrants conversation. The Editors and Editors-In-Chief will solicit such topics, but we invited the readership to submit ideas by contacting our managing editor at surgery@stellarmed.com. Topics must be pre-approved by the Editors-In-Chief as unsolicited submissions will not be considered. Debates and Dilemmas manuscripts should be 750 words or less and have a maximum of seven (7) references and no tables or figures.
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We are encouraging surgeons from developing countries to offer their perspectives and insight about surgical issues in their respective countries; this new article type will be managed by Dr. Anthony Charles. Insights into Global Surgery articles will not include an abstract; they must be 750 words or less; they may have a maximum of ten references; and they may contain one figure.

Letters to the Editor
Letters to the editor must be in response to previously published articles in Surgery. Letters not pertaining to previously published Surgery articles will not be considered. Each letter must not exceed 500 words, should be typed with double-spacing, and may include five (5) references and no figures

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Societal Papers
Scientific work presented at annual meetings of the Academic Surgical Congress (ASC) under the auspices of the Society of University Surgeons (SUS), Central Surgical Association (CSA), and American Association of Endocrine Surgeons (AAES) should follow the guidelines for Original Communications. The title page should also include the meeting name, location, and dates and type of presentation. Any additional material must be designated as Supplement Material outlined clearly as "For the online version of the article, not to be included in the print version."

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A structured abstract of no more than 250 words must accompany the manuscript and consist of four paragraphs, each with its introductory label: Background (stating the purpose of the study), Methods, Results, and Conclusions. This abstract should follow the title page and should be numbered page two of the manuscript. Abstracts are only necessary for Original Communications, Societal papers, and Reviews.

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For the main text, authors should refer to the brief description of types of submissions as well as the requirements on reporting of institutional ethics approval or exemption, informed consent, patient details, human trial registration and animal/human experiments. Authors should also include a statement regarding study limitations at the end of the Discussion.

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4. Figures (Optional)
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The STROCSS 2019 Guideline		
Item no.	**Item description**	**Page**
TITLE		
1	Title: - The word cohort or cross-sectional or case-controlled is included - The area of focus is described (e.g. disease, exposure/intervention, outcome) - Key elements of study design are stated (e.g. retrospective or prospective)	1
ABSTRACT		
2a	Introduction: the following points are briefly described - Background - Scientific Rationale for this study	2
2b	Methods: the following areas are briefly described - Study design (cohort, retro-/prospective, single/multi-centred) - Patient populations and/or groups, including control group, if applicable - Interventions (type, operators, recipients, timeframes) - Outcome measures	2
2c	Results: the following areas are briefly described - Summary data (with statistical relevance) with qualitative descriptions, where appropriate	2
2d	Conclusion: the following areas are briefly described - Key conclusions - Implications to practice - Direction of and need for future research	2
INTRODUCTION		
3	Introduction: the following areas are described in full - Relevant background and scientific rationale - Aims and objectives - Research question and hypotheses, where appropriate	4-5
METHODS		
4a	Registration and ethics - Research Registry number is stated, in accordance with the declaration of Helsinki* - All studies (including retrospective) should be registered before submission *"*Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject*" (this can be obtained from: ResearchRegistry.com or ClinicalTrials.gov or ISRCTN)	6
4b	Ethical Approval: the following areas are described in full - Necessity for ethical approval - Ethical approval, with relevant judgement reference from ethics committees - Where ethics was unnecessary, reasons are provided	6
4c	Protocol: the following areas are described comprehensively - Protocol (*a priori* or otherwise) details, with access directions - If published, journal mentioned with the reference provided	6

4d	Patient Involvement in Research - Describe how, if at all, patients were involved in study design e.g. were they involved on the study steering committee, did they provide input on outcome selection, etc.	6
5a	Study Design: the following areas are described comprehensively - 'Cohort' study is mentioned - Design (e.g. retro-/prospective, single/multi-centred)	6
5b	Setting: the following areas are described comprehensively - Geographical location - Nature of institution (e.g. academic/community, public/private) - Dates (recruitment, exposure, follow-up, data collection)	6
5c	Cohort Groups: the following areas are described in full - Number of groups - Division of intervention between groups	NA
5d	Subgroup Analysis: the following areas are described comprehensively - Planned subgroup analyses - Methods used to examine subgroups and their interactions	NA
6a	Participants: the following areas are described comprehensively - Eligibility criteria - Recruitment sources - Length and methods of follow-up	6
6b	Recruitment: the following areas are described comprehensively - Methods of recruitment to each patient group - Period of recruitment	6
6c	Sample Size: the following areas are described comprehensively - Margin of error calculation - Analysis to determine study population - Power calculations, where appropriate	NA
INTERVENTION AND CONSIDERATIONS		
7a	Pre-intervention Considerations: the following areas are described comprehensively - Patient optimisation (pre-surgical measures) - Pre-intervention treatment (hypothermia/-volaemia/-tension; ICU care; bleeding problems; medications)	6-7
7b	Intervention: the following areas are described comprehensively - Type of intervention and reasoning (e.g. pharmacological, surgical, physiotherapy, psychological) - Aim of intervention (preventative/therapeutic) - Concurrent treatments (antibiotics, analgaesia, anti-emetics, NBM, VTE prophylaxis) - Manufacturer and model details where applicable	9
7c	Intra-Intervention Considerations: the following areas are described comprehensively - Administration of intervention (location, surgical details, anaesthetic, positioning, equipment needed, preparation, devices, sutures, operative time) - Pharmacological therapies include formulation, dosages, routes and durations - Figures and other media are used to illustrate	NA

7d	Operator Details: the following areas are described comprehensively - Training needed - Learning curve for technique - Specialisation and relevant training	NA
7e	Quality Control: the following areas are described comprehensively - Measures taken to reduce variation - Measures taken to ensure quality and consistency in intervention delivery	NA
7f	Post-Intervention Considerations: the following areas are described comprehensively - Post-operative instructions and care - Follow-up measures - Future surveillance requirements (e.g. imaging, blood tests)	6-7
8	Outcomes: the following areas are described comprehensively - Primary outcomes, including validation, where applicable - Definitions of outcomes - Secondary outcomes, where appropriate - Follow-up period for outcome assessment, divided by group	7
9	Statistics: the following areas are described comprehensively - Statistical tests, packages/software used, and interpretation of significance - Confounders and their control, if known - Analysis approach (e.g. intention to treat/per protocol) - Sub-group analysis, if any	7-8
RESULTS		
10a	Participants: the following areas are described comprehensively - Flow of participants (recruitment, non-participation, cross-over and withdrawal, with reasons) - Population demographics (prognostic features, relevant socioeconomic features, and significant numerical differences)	9-10
10b	Participant Comparison: the following areas are described comprehensively - Table comparing demographics included - Differences, with statistical relevance - Any group matching, with methods	9-10 21-23
10c	Intervention: the following areas are described comprehensively - Changes to interventions, with rationale and diagram, if appropriate - Learning required for interventions - Degree of novelty for intervention	NA
11a	Outcomes: the following areas are described comprehensively - Clinician-assessed and patient-reported outcomes for each group - Relevant photographs and imaging are desirable - Confounders to outcomes and which are adjusted	9-10
11b	Tolerance: the following areas are described comprehensively - Assessment of tolerance - Loss to follow up, with reasons (percentage and fraction) - Cross-over with explanation	NA
11c	Complications: the following areas are described comprehensively - Adverse events described - Classified according to Clavien-Dindo classification*	9-10

	- Mitigation for adverse events (blood loss, wound care, revision surgery should be specified) *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. 2004; 240(2): 205-213	
12	Key Results: the following areas are described comprehensively - Key results, including relevant raw data - Statistical analyses with significance	9-10
DISCUSSION		
13	Discussion: the following areas are described comprehensively - Conclusions and rationale - Reference to relevant literature - Implications to clinical practice - Comparison to current gold standard of care - Relevant hypothesis generation	11-14
14	Strengths and Limitations: the following areas are described comprehensively - Strengths of the study - Limitations and potential impact on results - Assessment of bias and management	14
15	Implications and Relevance: the following areas are described comprehensively - Relevance of findings and potential implications to clinical practice are detailed - Future research that is needed is described, with study designs detailed	14
CONCLUSION		
16	Conclusions: - Key conclusions are summarised - Key directions for future research are summarised	15
DECLARATIONS		
17a	Conflicts of interest - Conflicts of interest, if any, are described	16
17b	Funding - Sources of funding (e.g. grant details), if any, are clearly stated	16

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	14
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions © Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed © Describe any sensitivity analyses	7-8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage © Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest © Summarise follow-up time (eg, average and total amount)	9 21-23
Outcome data	15*	Report numbers of outcome events or summary measures over time	9-10

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.