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Prediction models for adverse outcomes in vascular surgery

Modelos preditores de *outcomes* adversos em cirurgia vascular

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Dissertação de candidatura ao grau de Doutor apresentada à Faculdade de Medicina da Universidade do Porto, no âmbito do Programa Doutoral em Investigação Clínica e em Serviços de Saúde.

This PhD thesis has been submitted in fulfilment of the requirements for the PhD degree in Clinical and Health Services Research at the Faculty of Medicine of the University of Porto.

Título *(Title)*:

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Doutora Maria Isabel Amorim de Azevedo

TABLE OF CONTENTS

I. Acknowledgements

A combination of work, effort, determination, dedication, coordination, organization and collaboration resulted in this PhD thesis. Since it is not the work of a sole person I must recognize the contributions of my colleagues and supervisors, it was an honor and a privilege to work with them during this epic journey.

I would like to thank my supervisor, Professor Doutor Fernando Abelha, for being my mentor and professor, for the supervision and guidance along the way. I also thank my co-supervisor, Professora Doutora Joana Mourão, for all her motivation and new perspectives. I would like to express my most deep admiration for their contribution in the research of perioperative outcomes and all the encouragement provided to young anesthesiologists to perform clinical research.

I thank the teachers and tutors of the Harvard Medical School and Faculty of Medicine of the University of Porto for all they taught me. To Professor Doutor Altamiro Pereira I would like to thank the opportunity that he provided me. Moreover, I thank Professor Doutor Luís Azevedo, Professor Doutor Mário Dinis Ribeiro, Professor Doutor Armando Teixeira Pinto and Professor Doutor João Fonseca, for their essential teachings.

I also thank the research team that collaborated with me throughout this project, namely, Ana Isabel Lopes, Diana Leite, João Moreira, Leonor Mendes, Sofia Ferraz and Tânia Amaral. I thank all members of the Vascular Surgery Department and Anesthesiology Department of Centro Hospitalar de São João, who helped me during these years, especially my dear colleague Luís Guimarães Pereira.

I would like to thank all patients, for their unengaged and anonymous participation in this research; ultimately, they are the reason for all our work.

I would like to thank my family and close friends for the encouragement and constant support, specially my best friend and wife, Marina. Without you, this thesis would not have been possible.

II. List of publications

This PhD thesis is based in the following publications:

A) Pedro Videira Reis, Mariana Morgado, Inês Valdoleiros, Marina Dias Neto, Joana Mourão. Complications of Endovascular Aneurysm Repair: Mortality, Myocardial Infarction and Acute Kidney Injury. Turkish Journal of Anaesthesioly and Reanimation 2018;46:222-8

B) Pedro Videira Reis, Ana Isabel Lopes, Diana Leite, João Moreira, Leonor Mendes, Sofia Ferraz, Tânia Amaral, Fernando Abelha. Predicting mortality in patients admitted to the Intensive Care Unit after open Vascular Surgery. Surgery Today 2019;49(10):836-842

C) Pedro Videira Reis, Ana Isabel Lopes, Diana Leite, João Moreira, Leonor Mendes, Sofia Ferraz, Tânia Amaral, Joana Mourão, Fernando Abelha. Major Cardiac Events in Patients Admitted to Intensive Care After Vascular Noncardiac Surgery: A Retrospective Cohort. Seminars in Cardiothoracic and Vascular Anesthesia 2019;23(3):293-299

D) Pedro Reis, Ana Isabel Lopes, Diana Leite, João Moreira, Leonor Mendes, Sofia Ferraz, Tânia Amaral, Fernando Abelha. Incidence, predictors and validation of risk scores to predict postoperative mortality after noncardiac vascular surgery, a prospective cohort study. International Journal of Surgery 2020;73:89-93

Pedro Reis, Ana Isabel Lopes, Diana Leite, João Moreira, Leonor Mendes, Sofia Ferraz, Tânia Amaral, Fernando Abelha. Major Cardiac Events After Vascular Noncardiac Surgery: A Prospective Study (in submission)

Pedro Reis, Diana Leite, Sara Fonseca, Maria Graça Afonso. Effectiveness and safety of epidural analgesia for postoperative pain management after vascular surgery: A retrospective cohort. Journal of Pain Management 2018;11(4):395-401 (related but not included in this PhD thesis)

III. Acronyms

AIDS: Acquired Immune Deficiency Syndrome

AHF: Acute Heart Failure

AKI: Acute Kidney Injury

AKIN: Acute Kidney Injury Network

APACHE: Acute Physiology And Chronic Health Evaluation

ASA: American Society of Anesthesiology

AUROC: Area Under Receiver Operating Characteristics Curve

BP: Blood Pressure

CABG: Coronary Artery Bypass Graft

CAPTA: Chronic Kidney Disease, Age, Peripheral Arterial Disease, Intraoperative Red Blood Cell Transfusion, Atrial Fibrillation

CCI: Age-adjusted Charlson Comorbidity Index

CEA: Carotid Endarterectomy

CI: Confidence Interval

CKD: Chronic Kidney Disease

COPD: Chronic Obstructive Pulmonary Disease

CPE: Cardiogenic Pulmonary Edema

CVP: Central Venous Pressure

eGFR: estimated Glomerular Filtration Rate

ESA: European Society of Anesthesiology

ESC: European Society of Cardiology

EVAR: Endovascular Aneurysm Repair

ICU: Intensive Care Unit

IHD: Ischemic Heart Disease

KDIGO: Kidney Disease Improving Global Outcomes

LOS: Length Of Stay

MACE: Major Adverse Cardiac Events

MDRD: Modification of Diet in Renal Disease

METs: Metabolic Equivalents

MI: Myocardial Infarction

NSQIP: National Surgical Quality Improvement Program

OR: Odds Ratio

PAD: Peripheral Arterial Disease

PCI: Percutaneous Coronary Intervention

POSPOM: Preoperative Score to Predict Postoperative Mortality

RBC: Red Blood Cells

RIFLE: Risk, Injury, Failure, Loss, End Stage Renal Disease

RRT: Renal Replacement Therapy

SAPS: Simplified Acute Physiology Score

SAVS-CRI: South African Vascular Surgical Cardiac Risk Index

STROCSS: Strengthening The Reporting Of Cohort Studies In Surgery

TRIPOD: Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis

V-POSSUM: Vascular-Physiological And Operative Severity Score For The enUmeration Of Mortality And Morbidity

VQI-CRI: Vascular Quality Initiative Cardiac Risk Index

VS: Noncardiac Vascular Surgery

VSG-CRI: Vascular Study Group of New England Cardiac Risk Index

1. Summary

1.1 Introduction

Autonomic and humoral response to surgical stress together with patient position, temperature management, bleeding and type of anesthesia may contribute to hemodynamic changes leading to myocardial ischemia and heart failure. Perioperative risk assessment and management is essential as recommended by the European Society of Cardiology (ESC)/European Society of Anaesthesiology (ESA) joint guidelines. Vascular Surgery (VS) patients have cardiovascular risk factors that are associated with mortality, Major Adverse Cardiac Events (MACE) or other complications.

Mortality prediction is important not only after surgery but also after Intensive Care (ICU) admission. The Acute Physiology And Chronic Health Evaluation (APACHE) and the Simplified Acute Physiology Score (SAPS) are used to calculate in-hospital mortality after ICU admission. The Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (POSSUM) and the Preoperative Score to Predict Postoperative Mortality (POSPOM) focus on mortality until 30-days after surgery. The Surgical Apgar Score includes only three variables and has been used in noncardiac surgery with acceptable results. Age-adjusted Charlson Comorbidity Index (CCI) estimates the 10-year mortality according to patients' comorbidities.

Perioperative cardiac complications depend on patient and surgery-related risk factors. Myocardial injury is often undetected because it may not exhibit typical symptoms of ischemia. Lee Revised Cardiac Risk Index (RCRI) uses six independent variables to predict the probability of MACE after noncardiac surgery. Vascular Quality Initiative (VQI-CRI), Vascular Study Group of New England (VSG-CRI) and South African Vascular Surgical (SAVS-CRI) Cardiac Risk Indexes were derived to predict MACE after VS.

Postoperative Acute Kidney Injury (AKI) is divided in 3 stages of dysfunction based on Creatinine increase, urine output decrease or the need of renal replacement therapy (RRT). In aortic procedures, embolization/trauma/occlusion of renal vessels, iodinated contrast, inflammatory/ischaemic response after surgery have been suggested to play a part. Vascular Surgery Kidney Injury Predictive Score (VSKIPS) Model 1 (pre) or Model 2 (pre and intraoperative variables) fairly predict AKI after major open VS.

1.2 Aims

To study perioperative risk factors for mortality (Papers A, B, D) and adverse outcomes (Papers A, C) after VS and their association with hospital length of stay. To compare the accuracy and discriminative power of different models to predict postoperative mortality or complications after VS (Papers B, C, D). Identification of a simple, objective, accurate risk stratification score with good discriminative power to allow better care and resource management (Papers C, D).

1.3 Methods

In paper A, we analyzed mortality and adverse outcomes after Endovascular Aneurysm Repair (EVAR). In papers B and C, we analyzed mortality or MACE in patients admitted to ICU after VS. In papers A to C, we used logistic regression to identify risk factors. In paper D, we prospectively collected mortality after elective VS and used Cox regression. To reduce overfitting, we selected the leave-one-out cross-validation approach and the bootstrapping method. We performed Bonferroni correction for multiple comparisons. We compared the area under the curve (AUC) of our models with existing scores.

1.4 Results/Discussion

Postoperative 30-day mortality after EVAR was 2%. The ESC/ESA guidelines consider EVAR an intermediate risk surgery with a 30-day cardiovascular mortality of 1-5%. Hospital mortality in paper B was 5%, 1.3% after intermediate and 8.4% after high-risk surgery. Age, smoking, high-risk surgery, serum sodium, urea and leukocyte count at ICU admission were independent predictors while hematocrit after surgery was considered a protective factor. The AUC of our model was 0.86 compared to 0.75 of SAPS, 0.77 of APACHE, 0.80 of POSPOM and 0.83 of V-POSSUM. Postoperative 30-day mortality after elective VS was 6%. Age, peripheral arterial disease, chronic kidney disease, atrial fibrillation and intraoperative transfusion were independent risk factors. The AUC of our model was 0.83 (pre) or 0.88 (pre and intraoperative variables) similar to 0.86 of V-POSSUM, superior to 0.78 of POSPOM and 0.73 of CCI. In both papers B and D, the observed mortality was similar to predicted by POSPOM or V-POSSUM and in line with previous studies.

The incidence of Myocardial Infarction (MI) after EVAR was 5%, the superior cutoff value of ESC/ESA guidelines. In paper C, we observed 81 MACE in 60 patients (incidence of 6.5%). Regarding MI, the incidence was 3.0% (1.5% after intermediate and 4.6% after high-risk surgery). Previous history of Ischemic Heart Disease (IHD), atrial fibrillation, insulin-treated *diabetes mellitus*, mechanical ventilation, and heart rate at admission to ICU were considered independent predictors. Insulin-treated *diabetes mellitus* patients and IHD are included in RCRI and VSG, whereas VQI and SAVS include all diabetic patients. The AUC of our model was 0.79 (0.77 after leave-one-out cross-validation and bootstrapping or 0.71 if excluding the postoperative variables) compared to RCRI (0.66), VSG-CRI (0.69), VQI-CRI (0.71) and SAVS-CRI (0.73). Applying our model without the two postoperative variables to paper D database resulted in an AUC of 0.82.

Incidence of AKI after EVAR was 18%. Preoperative serum urea, general anesthesia and surgery duration were considered independent predictors in multivariate analysis. The AUC of our study, including postoperative variables was 0.88 compared to 0.72 of VSKIPS model 1 and 0.79 of VSKIPS model 2. We had one variable in common with VSKIPS, procedure duration, which may indicate more complex surgery and more intravenous (IV) contrast. Incidence of AKI in patients admitted to ICU after VS was 5.0% (4.1% in intermediate and 5.9% after high-risk surgery). After endovascular surgery, the incidence was 10.6%. In addition to IV contrast, peri-renal manipulation or stent fixation, microembolization, renal artery occlusion, inflammatory/ischaemic response after endovascular approach have been suggested to play a part. Incidence of AKI in paper D database was 9.8%. In that prospective study, we also collected the postoperative urinary output and acute RRT. These data will be the subject of future studies.

The database used for papers B and C was registered prospectively. Surgical complications may have affected the adverse outcomes we measured. Regarding AKI, we could not collect the amount of IV contrast used, AKI preventive strategies or the postoperative urinary output. We consider that using bootstrapping and cross validation is not ideal, however, it is an acceptable way to randomly test our scores. We performed time-to-event analysis and consider it important, even if no differences were found. Despite including some postoperative variables, we believe our models are simple, can be useful in different circumstances and will be more accurately validated in the future.

1.5 Future perspectives and conclusions

Postoperative adverse events may be used as a measurement of quality of care. Pulmonary complications or surgical site infection after surgery are also under study. High-risk patients may benefit from careful planning, prevention strategies, clinical optimization, intraoperative monitoring and longer follow-up. Biomarkers such as high sensitivity C Reactive Protein, Copeptin, Survivin, Brain Natriuretic Peptide are being used to early detect complications and improve the performance of risk scores.

Incidence of mortality, MACE and AKI was within the range of previous studies. Perioperative adverse events increased the risk of other complications or mortality and extended the length of stay. This thesis discusses the best evidence regarding risk scores to predict mortality and morbidity after VS. Incidence of perioperative complications may escalate in the future with increasing age and comorbidities. Preoperative evaluation is a key factor but intra and postoperative monitoring should also be adequate. Targeted interventions to early detect and treat complications are important to decrease the incidence and impact of these adverse events.

2. Resumo

2.1 Introdução

A resposta autonómica e humoral ao stress cirúrgico, juntamente com posicionamento, controlo da temperatura, hemorragia e tipo de anestesia, podem contribuir para alterações hemodinâmicas e levar a isquemia miocárdica. A avaliação e gestão de risco perioperatório é recomendada pelas *guidelines* da Sociedade Europeia de Cardiologia (ESC)/Sociedade Europeia de Anestesiologia (ESA). Doentes propostos para cirurgia vascular (CV) apresentam fatores de risco cardiovascular associados a mortalidade, eventos cardíacos adversos (MACE) ou outras complicações. A detecção precoce de doentes em risco pode diminuir a incidência e impacto desses eventos adversos.

Prever mortalidade é importante não apenas após cirurgia, mas também após admissão em Cuidados Intensivos (UCI). O *Acute Physiology And Chronic Health Evaluation* (APACHE) e o *Simplified Acute Physiology Score* (SAPS) são utilizados para calcular mortalidade hospitalar após admissão em UCI. O *Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity* (POSSUM) e o *Preoperative Score to Predict Postoperative Mortality* (POSPOM) focam-se na mortalidade até 30 dias após cirurgia. O *Surgical Apgar* inclui apenas 3 variáveis e tem tido resultados aceitáveis em cirurgia não cardíaca. O *Charlson Comorbidity Index* (CCI) ajustado à idade estima a mortalidade a 10 anos de acordo com as comorbilidades dos doentes.

Complicações cardíacas perioperatórias dependem de fatores do doente e da cirurgia. A lesão miocárdica pode não ser detetada pois não apresenta sintomas isquémicos típicos. O Lee *Revised Cardiac Risk Index* (RCRI) usa 6 variáveis independentes para prever MACE após cirurgia não cardíaca. O *Vascular Quality Initiative* (VQI-CRI), o *Vascular Study Group of New England* (VSG-CRI) e o *South African Vascular Surgical* (SAVS-CRI) *Cardiac Risk Indexes* foram derivados para prever MACE após CV.

A lesão renal aguda pós-operatória (LRA) é dividida em 3 estadios, com base no aumento da creatinina, diminuição do débito urinário ou necessidade de técnica de substituição renal (TSR). Em procedimentos aórticos, a embolização/trauma/oclusão de vasos renais, o contraste iodado, a resposta inflamatória/isquémica após cirurgia foram sugeridos como fatores importantes. O Vascular Surgery Kidney Injury Predictive Score (VSKIPS) Modelo 1 (pré) ou Modelo 2 (variáveis pré e intraoperatórias) tem razoável capacidade para prever LRA após CV major aberta.

2.2 Objetivos

Avaliação de fatores de risco para mortalidade (Artigos A, B, D) e eventos adversos (Artigos A, C) após CV e o seu impacto no tempo de internamento. Comparar a precisão e o poder discriminativo de modelos preditores do risco de complicações e mortalidade pós-operatória em CV (Artigos B, C, D). 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 (Artigos C, D).

2.3 Metodologia

No artigo A, analisamos mortalidade e eventos adversos após correção endovascular de aneurisma (EVAR). Nos artigos B e C, analisamos mortalidade ou MACE nos doentes admitidos em UCI após CV. Nos artigos A a C, usamos regressão logística para identificar fatores de risco. No artigo D, recolhemos prospetivamente a mortalidade após CV eletiva e usamos a regressão de Cox. Para reduzir a possibilidade de sobreajustamento, utilizamos validação cruzada *leave-one-out* e *bootstrapping*. Usamos a correção de Bonferroni para comparações múltiplas. Comparamos os nossos modelos com os scores existentes analisando a área sob a curva (AUC).

2.4 Resultados/Discussão

A mortalidade aos 30 dias após EVAR foi de 2%. As *guidelines* ESC/ESA consideram o EVAR uma cirurgia de risco intermédio, com mortalidade 1-5%. A mortalidade hospitalar no artigo B foi de 5%, 1,3% após risco intermédio e 8,4% após cirurgia de alto risco. Idade, tabagismo, cirurgia de alto risco, sódio sérico, ureia e contagem de leucócitos à admissão na UCI foram preditores independentes, enquanto o hematócrito após a cirurgia foi considerado um fator protetor. A AUC do nosso estudo foi de 0,86 em comparação com 0,75 do SAPS, 0,77 do APACHE, 0,80 do POSPOM e 0,83 do V-POSSUM. A mortalidade aos 30 dias após CV eletiva foi de 6%. Idade, doença arterial periférica, doença renal crónica, fibrilação atrial e transfusão intraoperatória foram fatores de risco independentes. A AUC no nosso estudo foi de 0,83 (variáveis pré) ou 0,88 (pré e intraoperatórias) que comparam com 0,86 do V-POSSUM, 0,78 do POSPOM e 0,73 do CCI. Nos artigos B e D, a mortalidade observada foi semelhante à prevista pelo POSPOM ou V-POSSUM e de acordo com estudos anteriores.

A incidência de enfarte do miocárdio (EAM) após EVAR foi de 5%, o limite superior das *guidelines* ESC/ESA. No artigo C, observamos 81 MACE em 60 pacientes (incidência de 6.5%). A incidência de EAM foi de 3.0% (1.5% após intermédio e 4.6% após cirurgia de alto risco). História de cardiopatia isquémica (CI), fibrilação auricular, *diabetes mellitus* tratados com insulina, ventilação mecânica e frequência cardíaca à admissão na UCI foram considerados preditores independentes. Doentes com *Diabetes mellitus* tratados com insulina e CI estão incluídos no RCRI e no VSG, enquanto o VQI e o SAVS incluem todos os doentes diabéticos. A AUC do nosso estudo foi de 0,79 (0,77 após validação cruzada e *bootstrapping* ou 0,71 se excluídas as variáveis pós-operatórias) comparada com RCRI (0,66), VSG-CRI (0,69), VQI-CRI (0,71) e SAVS-CRI (0,73). Aplicando nosso modelo à base de dados D, sem as duas variáveis pós-operatórias, obtemos uma AUC de 0,82.

A incidência de LRA após EVAR foi de 18%. Ureia sérica pré-operatória, anestesia geral e duração da cirurgia foram considerados preditores independentes. A AUC do nosso estudo incluindo variáveis pós-operatórias foi 0,88 em comparação com 0,72 do VSKIPS modelo 1 e 0,79 do VSKIPS modelo 2. A duração do procedimento é comum ao VSKIPS o que pode indicar cirurgia complexa e mais contraste intravenoso (IV). A incidência de LRA nos doentes admitidos em UCI após CV foi de 5,0% (4,1% após intermédio e 5,9% após cirurgia de alto risco). Na cirurgia endovascular, a incidência foi de 10,6%. Além do contraste IV, a manipulação/fixação peri-renal de stent, microembolização, oclusão de artérias renais, resposta inflamatória/isquémica após abordagem endovascular são hipóteses possíveis. A incidência de LRA na base de dados do artigo D foi de 9,8%. Nesse estudo prospectivo, também registamos o débito urinário e a necessidade de TSR.

A base de dados usada nos artigos B e C foi registada prospetivamente. Complicações cirúrgicas podem estar relacionadas com eventos adversos. Em relação à LRA, não foi possível recolher a quantidade de contraste IV utilizado, estratégias preventivas ou o débito urinário pós-operatório. Consideramos que o uso de *bootstrapping* e validação cruzada não é ideal; no entanto, é uma maneira aceitável de testar aleatoriamente os nossos scores. Realizamos análise *time-to-event* que consideramos importante, embora não se tenham observado grandes diferenças. Apesar de alguns incluírem variáveis pós-operatórias, acreditamos que nossos modelos são simples, podem ser úteis em determinadas circunstâncias e deverão ser futuramente validados com maior exatidão.

2.5 Perspectivas futuras e conclusões

Eventos adversos pós-operatórios podem ser usados para medição da qualidade dos cuidados de saúde. Complicações pulmonares ou infecção do local cirúrgico após cirurgia também se encontram em estudo. Doentes de alto risco podem beneficiar de melhor planeamento, estratégias de prevenção, otimização clínica, monitorização intraoperatória e *follow-up* mais prolongado. Biomarcadores como Proteína C Reativa de alta sensibilidade, Copeptina, Survivina, *Brain Natriuretic Peptide* têm sido utilizados para detetar precocemente complicações e melhorar o desempenho dos scores de estratificação de risco.

As incidências de mortalidade, MACE e LRA ficaram dentro do previsto por estudos anteriores. Eventos adversos perioperatórios aumentaram o risco de outras complicações ou mortalidade e prolongaram o tempo de internamento. Esta tese discute a evidência científica existente sobre scores de risco para prever mortalidade e morbilidade após CV. A incidência de complicações perioperatórias pode crescer no futuro devido ao aumento da idade e das comorbilidades dos doentes propostos para CV. A avaliação pré-operatória é um fator-chave, mas a monitorização intra e pós-operatória também deve ser adequada. Intervenções direcionadas para detetar e tratar precocemente as complicações podem ser importantes para diminuir a incidência e o impacto desses eventos adversos.

3. Introduction

3.1 The evolution of risk stratification scores and severity of illness models

In 1941, the American Society of Anesthesiologists (ASA) asked a committee to study, examine, and devise a system to classify the ability of a patient to withstand anesthesia. The term "Operative Risk" was being used at the time with that objective but the experts thought that this estimation was complex and subjective. Saklad *et al*. tried to simplify by defining the "physical state" of the patient in 6 categories ranging from a healthy person (class 1) to one with an extreme systemic disorder that is an imminent threat to life (class 4). Emergency surgery categorized patients in class 5 if they were from classes 1-2 or class 6 if they were previously class 3-4.[1] In 1961, Dripps *et al.* recognized the association between the pre-operative physical status classification and postoperative mortality. Authors included the class 5 defined as a moribund patient who is not expected to survive for 24h with or without an operation and added the letter E to denote emergency surgery.[2] In 1980, a class 6 was added for those who were brainstem dead organ donors.[3]

The study of risk factors for postoperative complications continued with Goldman *et al.* in 1977.[4] They evaluated life-threatening and fatal cardiac complications after major noncardiac surgery. In multivariate analysis, 9 independent risk factors were identified: preoperative third heart sound or jugular venous distention; myocardial infarction in the preceding six months; more than five premature ventricular contractions per minute; rhythm other than sinus or presence of premature atrial contractions; age over 70 years; intraperitoneal, intrathoracic or aortic operation; emergency operation; important aortic stenosis; poor general medical condition.[4] Goldman was later a coauthor of the Lee Revised Cardiac Risk Index (RCRI).[5]

In addition to the models for the perioperative period, researchers begin to study mortality during and after Intensive Care Unit (ICU) stay. The Acute Physiology And Chronic Health Evaluation (APACHE) was first published in 1981[6] and later updated in 1985 (APACHE II),[7] 1991 (APACHE III)[8] and 2006 (APACHE IV).[9] The Simplified Acute Physiology Score (SAPS) was described in 1984,[10] updated in 1993 (SAPS II)[11] and 2005 (SAPS III).[12,13] Although APACHE was designed to measure severity of illness, both are calculated in the first 24h after ICU admission to predict in-hospital mortality.

3.2 General considerations

Every operation elicits a stress response initiated by tissue injury and mediated by neuroendocrine factors that may induce autonomic imbalance. Fluid shifts in the perioperative period add to the surgical stress and increase myocardial oxygen demand. Surgery also causes alterations in the balance between prothrombotic and fibrinolytic factors, potentially resulting in increased coronary thrombogenicity. The extent of such changes is proportionate to the extent and duration of the intervention. These factors, together with patient position, temperature management, bleeding, and type of anesthesia may contribute to hemodynamic derangements leading to myocardial ischemia and heart failure. Less invasive surgical and anesthetic techniques may reduce early mortality in patients at risk and limit postoperative complications.[14-16]

The European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA) guidelines on non-cardiac surgery for cardiovascular assessment and management recommend preoperative risk estimation.[17] Surgeries were divided in low (<1%), intermediate (1-5%) or high risk (>5%) for 30-day risk of cardiovascular death and myocardial infarction without considering patient's comorbidities.[17] Functional capacity measurement in Metabolic Equivalents (METs) is also recommended since it has a fair correlation with mortality, especially in thoracic surgery.[18,19] Guidelines ESC/ESA state that evidence for use of clinical risk indexes is currently Class I Level B.[17]

Older scores were designed for noncardiac surgery. However, Vascular Surgery (VS) patients have numerous cardiovascular risk factors that are associated with perioperative mortality and Major Adverse Cardiac Events (MACE).[20] Hemodynamic instability, blood loss, aortic cross clamping, reperfusion phenomena, and arterial embolism may increase the risk of adverse outcomes after VS.[21] Anesthetic and surgical techniques along with better planning and monitoring have decreased the intraoperative mortality.[22] Nevertheless, postoperative mortality is still frequent, predominantly in older patients and those who undergo major or emergent surgery, who have severe coexisting diseases or who develop complications.[23-26] Perioperative adverse outcomes may affect 12% of patients, a rate that tends to increase with age and comorbidities.[24,27,28] Adequate postoperative care allows for closer monitoring and early intervention to reduce complications and deaths.

Some models tried to predict not only mortality but also morbidity. This general postoperative morbidity models evaluate more frequently cardiovascular, renal or respiratory morbidity. Like mortality, these adverse outcomes are currently measured not only during hospital stay but until 30 days after surgery. Risk Scores analyzed in the papers of this thesis are described below (Tables 1 to 6). Some of them try to predict multiple outcomes so they may be included in more than one topic.

3.3 Risk Scores for mortality

Hospital mortality estimation by SAPS or APACHE after ICU stay has produced accurate results.[29-31] However, they focus on the severity of illness at admission, which may not be adequate for post-surgical patients.[32] The Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (POSSUM), described by Copeland *et al*, estimates 30-day mortality and morbidity after surgery using 12 pre and 6 intraoperative variables, making it difficult to use in preoperative planning and risk estimation.[33-36] The Portsmouth modification of POSSUM (P-POSSUM) improved its predictive ability and there is a variant specifically for VS patients, the Vascular POSSUM (V-POSSUM) with fair performance.[33-36] The disadvantage is that they only predict general morbidity.

The Preoperative Score to Predict Postoperative Mortality (POSPOM), from Le Manach *et al*, resulted in excellent estimation using 17 preoperative variables but its derivation cohort included many types of surgery.[37] The Surgical Apgar Score includes only three intraoperative variables (estimated blood loss, lowest mean arterial pressure, lowest hear rate) and is being used in noncardiac surgery with acceptable results.[38] Age-adjusted Charlson Comorbidity Index (CCI) estimates the 10-year mortality according to patients' comorbidities.[39] The American College of Surgeons National Surgical Quality Improvement Program (NSQIP) score was built to predict post-operative mortality and is available online, including a subset for use in VS, but the authors did not publish the equation making it unavailable for broad clinical research.[40,41] This score was derived from the 2007 dataset from 180 hospitals and validated with the 2008 dataset, both containing more than 200 000 patients and is recommended by ESC/ESA guidelines in pre-operative assessment. It allows the calculation of the probability of death; cardiac, renal, infectious or respiratory complications; readmission and Length of Stay (LOS).

Table 1: Simplified Acute Physiology Score (SAPS).[11]

	0 points	Abnormal value points				
Age (years)	<40	50-59 7 points	60-69 12 points	70-74 15 points	75-70 16 points	≥ 80 18 points
Heart Rate (bpm)	70-119	40-69 2 points	120-159 4 points	≥ 160 7 points	< 40 11 points	
Systolic BP (mmHg)	100-199	≥ 200 2 points	70-99 5 points	< 70 13 points		
Body temperature (ºC)	< 39	≥ 39 3 points				
PaO_2 (mmHg) if IMV		≥ 200 6 points	100-199 9 points	< 100 11 points		
Urinary output (L/day)	≥ 1	0.5-0.9 4 points	< 0.5 11 points			
BUN (mmol/L)	< 10	10-29.9 6 points	≥ 30 10 points			
WBC count (10^9/L)	1.0-19.9	≥ 20 3 points	< 1.0 12 points			
Potassium (mmol/L)	3-4.9	< 3 or ≥ 5 3 points				
Sodium (mmol/L)	125-144	≥ 145 1 point	< 125 5 points			
Bicarbonate (mmol/L)	≥ 20	15-19 3 points	< 15 6 points			
Bilirubin (µmol/L)	< 68.4	68.4-102.5 4 points	≥ 102.6 9 points			
Glasgow Coma Scale	14-15	11-13 5 points	9-10 7 points	6-8 13 points	< 6 26 points	

	0 points	Abnormal value points		
Chronic disease		Metastatic cancer 9 points	Hematological cancer 10 points	AIDS 17 points
Type of admission	Scheduled surgical	Medical 6 points	Unscheduled surgical 8 points	

AIDS: acquired immune deficiency syndrome | BP: Blood Pressure | bpm: beats per minute
BUN: Blood Urea Nitrogen | IMV: invasive mechanical ventilation | WBC: White Blood Cells

Table 2. Acute Physiology And Chronic Health Evaluation (APACHE).[7]

Physiologic Variable		+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature - rectal (°C)		≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9
Mean Arterial Pressure (mm Hg)		≥160	130-159	110-129		70-109		50-69		≤49
Heart Rate		≥180	140-179	110-139		70-109		55-69	40-54	≤39
Respiratory Rate (nonventilated or ventilated)		≥50	35-49		25-34	12-24	10-11	6-9		≤5
Oxygenation (mmHg) a. $FiO_2 > 0,5$ use A-aDO_2 b. $FiO_2 < 0,5$ use PaO_2	a	≥500	350-499	200-349		<200				
	b					> 70	61-70		55-60	<55
Arterial pH		≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
Serum Sodium (mmol/l)		≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
Serum Potassium (mmol/l)		≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
Serum Creatinine (mg/dl, Double point score for acute renal failure)		≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
Hematocrit (%)		≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20
White Blood Count (in 1000/mm³)		≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
Glasgow-Coma-Scale (GCS)		Score = 15 minus actual GCS								
Serum HCO_3 (venous, mmol/l, use if no ABGs)		≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15
A = Total Acute Physiology Score APS		Sum of the 12 individual variable points								
B = Age Points		**C = Chronic Health Points**								
≤44 years	0 points	If the patient has a history of severe organ system insufficiency or is immunocompromised assign points as follows:								
45-54 years	2 points									
55-64 years	3 points									
65-74 years	5 points	a. For nonoperative or emergency postoperative patients – 5 points								
≥75 years	6 points	b. For elective postoperative patients – 2 points								
APACHE II Score = Sum of A (APS points) + B (Age points) + C (Chronic Health points)										

(From: Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13(10):818-29)

Table 3. Vascular-Physiological And Operative Severity Score For The enUmeration Of Mortality And Morbidity (V-POSSUM).[33]

Physiologic Score	**1 point**	**2 points**	**4 points**	**8 points**
Age (years)	<60	61-70	>70	-
Cardiac status	Normal	Cardiac drugs or steroids	Edema, warfarin, borderline cardiomegaly	Increased CVP, cardiomegaly
Respiratory status	Normal	Dyspnea on exertion, mild COPD	Limiting dyspnea, moderate COPD	Dyspnea at rest, severe COPD
Electrocardiogram	Normal	-	Atrial fibrillation (rate 60–90)	Any other abnormality
Systolic BP (mmHg)	110 - 130	100 - 109 or 131 - 170	> 170 or 90 - 99	< 90
Heart Rate (bpm)	50 - 80	40 - 49 or 81 - 100	101 - 120	< 40 or > 120
Hemoglobin (g/dL)	13 - 16	11.5 - 12.9 or 16.1 - 17.0	10.0 - 11.4 or 17.1 - 18.0	< 10.0 or > 18.0
White blood cell count (10^9/L)	4.0 - 10.0	10.1 - 20.0 or 3.1 - 3.9	> 20.0 or < 3.1	-
Urea (mmol/L)	< 7.5	7.5 - 10.0	10.1 - 15.0	> 15.0
Sodium (mmol/L)	> 136	131 - 135	126 - 130	< 126
Potassium (mmol/L)	3.5 - 5	3.2 - 3.4 or 5.1 - 5.3	2.9 - 3.1 or 5.4 - 5.9	< 2.9 or > 5.9
Glasgow coma scale	15	12-14	9-11	<9
Surgical Score	**1 point**	**2 points**	**4 points**	**8 points**
Operative severity	Minor	Intermediate	Major	Major+
Multiple procedures	1	-	2	>2
Total blood loss (mL)	< 100	101 - 500	501 - 999	≥ 1000
Peritoneal soiling	None	Minor (serous fluid)	Local pus	Free bowel content, pus or blood
Presence of malignancy	None	Primary only	Nodal metastases	Distant metastases
Type of surgery	Elective	-	Urgent not emergent (<24h after admission)	Emergent (immediate surgery <2h)

COPD: Chronic Obstructive Pulmonary Disease; CVP: central venous pressure

Table 4 (next page): Preoperative Score to Predict Postoperative Mortality (POSPOM).[37]

Age	Pointed assigned
18-20	+0
21-25	+1
26-30	+2
31-35	+3
36-40	+4
41-45	+5
46-50	+6
51-55	+7
56-60	+8
61-65	+9
66-70	+10
71-75	+11
76-80	+12
81-85	+13
86-90	+14
91-95	+15
>95	+16

Comorbidity	Points assigned
Ischemic heart disease	+1
Cardiac arrhythmia or heart blocks	+1
Chronic heart failure or cardiomyopathy	+4
Peripheral vascular disease	+1
Dementia	+2
Cerebrovascular disease	+1
Hemiplegia	+4
Chronic obstructive pulmonary disease	+1
Chronic respiratory failure	+3
Chronic alcohol abuse	+4
Cancer	+4
Diabetes	+1
Transplanted organ(s)	+2
Preoperative chronic hemodialysis	+1
Chronic renal failure	+2

Planned Surgery	Points assigned
Endoscopic digestive	+0
Ophthalmologic	+0
Gynecologic	+6
Other orthopedic	+6
Interventional cardiorhythmology	+8
Arthroplasty and spine	+9
Ear, nose and throat (ENT)	+9
Minor urologic	+9
Plastic	+9
Major urologic	+12
Others surgery	+12
Minor hepatic	+12
Minor gastrointestinal	+13
Renal transplant	+13
Minor vascular	+13
Orthopedic trauma	+14
Major hepatic	+15
Thoracic	+15
Neuro	+15
Major vascular	+16
Major gastrointestinal	+16
Interventional neuroradiology	+17
Cardiac	+17
Transplant	+22
Multiple trauma related	+22

3.4 Risk Scores for cardiac events

Perioperative cardiac complications depend on patient-related risk factors, type of surgery and admission. Perioperative myocardial injury is often undetected because it may not exhibit typical symptoms of ischemia, such as chest pain, angina pectoris, or dyspnea.[42] Acute myocardial infarction (MI) after major VS may range from 0.3-36%.[43] This is why some authors suggest to measure troponins until 3-7 days after surgery in high-risk patients.[44] An accurate preoperative risk assessment is essential to guide patient management, allowing appropriate medical optimization, establish cardiac interventions and early detect possible complications.[45]

Lee index or RCRI, a modified version of the original Goldman score, was designed to predict postoperative MI, pulmonary edema, ventricular fibrillation or cardiac arrest, and complete heart block. This index is composed of 6 independent predictors: high-risk surgery (suprainguinal vascular, intrathoracic, or intraperitoneal procedures); history of Ischemic Heart Disease (IHD); history of Congestive Heart Failure; history of cerebrovascular disease; preoperative treatment with insulin and preoperative Chronic Kidney Disease (CKD) with serum creatinine >2.0 mg/dL.[5] Although extensively used, RCRI may not be the best model to predict MACE after VS.[46]

More recently, Vascular Quality Initiative (VQI-CRI),[47] Vascular Study Group of New England (VSG-CRI)[48] and South African Vascular Surgical (SAVS-CRI)[49] Cardiac Risk Indexes were derived to predict MACE after VS. Differences in the scores are summarized in Table 5 (extracted from Paper C). The VQI-CRI has five variants depending on the surgery performed: carotid endarterectomy (CEA), endovascular aneurysm repair (EVAR), open abdominal aortic aneurysm repair, supra and infra-inguinal bypass. Age, type of surgery, history of IHD, diabetes mellitus and creatinine concentration >1.8 mg/dL are included in all models. Only VQI-CRI uses critical limb ischemia, arterial hypertension, stress test status and body mass index as predictors whereas VSG-CRI and SAVS use chronic β-Blockers as a risk factor and previous coronary artery bypass graft/percutaneous intervention as protective.

Assessing the risk is of paramount importance in an era rife with concerns about variations in the quality of care and use of healthcare resources.

Table 5. Comparison of the different cardiac risk scores (points in parenthesis).

RCRI	VQI-CRI [a)]	VSG-CRI	SAVS-CRI
High-risk surgery (1) [b)]	Age	Age (2-4)	Age > 65 years (2)
Ischemic Heart Disease (1)	Ischemic Heart Disease	Ischemic Heart Disease (2)	Ischemic Heart Disease (2)
Congestive Heart Failure (1)	Congestive Heart Failure	Congestive Heart Failure (2)	Suprainguinal surgery (7)
Cerebrovascular Disease (1)	Chronic Obstructive Pulmonary Disease	Chronic Obstructive Pulmonary Disease (2)	Intermediate risk surgery (3)
Insulin treated Diabetes Mellitus (1)	Diabetes Mellitus	Insulin treated Diabetes Mellitus (1)	Diabetes Mellitus (2)
Chronic Kidney Disease (Creatinine >2.0 mg/dL) (1)	Chronic Kidney Disease (Creatinine >1.8 mg/dL)	Chronic Kidney Disease (Creatinine >1.8 mg/dL) (2)	β-Blocker therapy (4)
	Critical limb ischemia	β-Blocker therapy (1)	CABG or PCI (-3)
	Arterial hypertension	Active smoker (1)	
	Abnormal cardiac stress test	CABG or PCI (-1)	
	Body Mass Index		

CABG: Coronary Artery Bypass Graft. PCI: Percutaneous Coronary Intervention.
[a)] Included variables and their relative weight is dependent on type of surgery.
[b)] Suprainguinal vascular, intrathoracic, or intraperitoneal procedures

3.5 Risk Scores for renal and other complications

Measurement of other types of complications is slightly more complex. We can calculate the estimated Glomerular Filtration Rate (eGFR) by using two formulas: the Cockcroft–Gault or the Modification of Diet in Renal Disease (MDRD). Unfortunately, most risk scores still use serum Creatinine levels instead of eGFR. There are several criteria for postoperative Acute Kidney Injury (AKI), commonly defined as an abrupt (1-7 days) and sustained (>24h) decrease in kidney function. Most experts agree that there are 3 stages of perioperative renal dysfunction based on Creatinine increase or urine output decrease (Table 8).[50-52]

Risk factors for the development of postoperative AKI following non-cardiac surgery have been evaluated, and include age >56 years, male sex, active cardiac failure, presence of ascites, hypertension, emergency surgery, intraperitoneal surgery, preoperative creatinine elevation and diabetes mellitus. Patients with ≥6 of these factors have a 10% incidence of AKI, and a hazard ratio of 46.2 compared to those with <3 risk factors.[53] In aortic procedures, microembolization into the renal vasculature, suprarenal bare stent fixation with the risk of renal artery trauma, accessory renal artery occlusion and the inflammatory and ischaemic response after endovascular manipulation have been suggested to play a part.[54-56] In addition to these factors, vascular surgeons may use iodinated contrast during diagnostic and interventional endovascular procedures that increase the risk of postoperative AKI. Identification of patients at risk of perioperative worsening of renal function is important to initiate supportive measures such as maintenance of adequate intravascular volume for renal perfusion and vasopressor use.[57]

In 2015, Kashani *et al.* presented a risk prediction score for AKI in patients submitted to open aortic VS. Two clinical multivariate models for the Vascular Surgery Kidney Injury Predictive Score (VSKIPS) were developed (Table 9). Model 1 was restricted to preoperative variables (preoperative glomerular filtration rate, history of previous vascular intervention and preoperative exposure to diuretics or β-Blockers), whereas model 2 included all the above and also age and intraoperative variables (duration of the procedure, fluid balance, fresh-frozen plasma and platelet transfusion). Both scores had a fair performance predicting the occurrence of postoperative AKI after major open vascular surgery of the descending thoracic or abdominal aorta.[58]

Respiratory complications after VS also started to gain attention recently. Alongside with cardiac comorbidities, many VS patients are smokers or have Chronic Obstructive Pulmonary Disease, increasing risk for respiratory adverse outcomes. Developing these complications in the postoperative period increase the risk of death or discharge to a nursing facility. The score created by Johnson *et al.* using the NSQIP database identified 12 independent predictors and had a good performance.[59] Genovese *et al.* also published risk factors for adverse respiratory events after VS using the Vascular Quality Initiative database.[60]

Table 6. Age-adjusted Charlson Comorbidity Index (CCI).[39]

Age	(1 point per decade) ≥50 years
Human Immunodeficiency virus Metastatic Solid Tumor	6 points
Non-metastatic Solid Tumor Malignant Lymphoma Leukemia Diabetes with end organ damage Moderate to severe Kidney Disease Hemiplegia	2 points
Diabetes without end organ damage Mild liver disease Ulcer disease Connective tissue disease Chronic Pulmonary disease Cerebrovascular disease Dementia Peripheral vascular disease Congestive Heart Failure Myocardial Infarction	1 point

Table 7. Kidney Disease Improving Global Outcomes (KDIGO) criteria for Postoperative Acute Kidney Injury (AKI) diagnosis.[50]

	Serum Creatinine criteria	Urine Output criteria
Stage 1	Creatinine 1.5-1.9x baseline Creatinine increase ≥0.3 mg/dL	<0.5 ml/kg/h for 6h
Stage 2	Creatinine 2-2.9x baseline	<0.5 ml/kg/h for 12h
Stage 3	Creatinine >3x baseline Creatinine ≥4 mg/dl Need for RRT	<0.3 ml/kg/h for 24h or anuria for 12h

RRT: Renal Replacement Therapy

Class	RIFLE SCr or GFR	Stage	AKIN SCr	Stage	KDIGO SCr
Risk	Increased Scr x 1.5 or GFR decrease > 25% (within 7 days)	1	Increase in SCr ≥ 0.3 mg/dL or ≥ 150% to 200% (1.5- to 2-fold) from baseline (within 48 hours)	1	Increase in SCr by ≥ 0.3 mg/dL within 48 hours or increase in SCr 1.5 to 1.9 times baseline which is known or presumed to have occurred within the prior 7 days
Injury	Increased Scr x 2.0 or GFR decrease > 50%	2	Increase in SCr to more than 200% to 300% (> 2- to 3-fold) from baseline	2	Increase in SCr to 2.0 to 2.9 times baseline
Failure	Increased Scr x 3.0 or GFR decrease > 75% or SCr ≥ 4.0 mg/dL or acute increase ≥ 0.5 mg/dL	3	Increase in SCr to more than 300% (> 3-fold) from baseline or SCr ≥ 4.0 mg/dL with an acute increase of at least 0.5 mg/dL or initiation of renal replacement therapy	3	Increase in SCr to 3.0 times baseline or increase in SCr to ≥ 4.0 mg/dL or initiation of renal replacement therapy
Loss	Persistent acute renal failure = complete loss of kidney function > 4 weeks				
End Stage Kidney Disease	End stage of kidney disease (> 3 months)				

Modified from Bellomo et al.[52], Mehta et al.[51] and Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group[50]

Table 8 (previous page): Comparison of Risk, Injury, Failure, Loss or End Stage Kidney Disease (RIFLE), Acute Kidney Injury Network (AKIN) and Kidney Disease Improving Global Outcomes (KDIGO) criteria for postoperative Acute Kidney Injury diagnosis based on Serum Creatinine (SCr), estimated Glomerular Filtration Rate (GFR) or Urine Output.

Table 9. Vascular Surgery Kidney Injury Predictive Score (VSKIPS).[58]

	Model 1			Model 2		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Preoperative eGFR	0.8	0.7-0.8	<0.001	0.8	0.7-0.9	<0.001
Previous intervention	1.8	1.1-2.9	0.03	1.3	0.7-2.2	0.4
Preoperative diuretics	1.3	0.9-1.8	0.08	1.3	0.9-1.8	0.14
Preoperative β-Blocker	1.38	0.99-1.9	0.055	1.4	0.98-1.9	0.06
Age (per year)				1.003	0.98-1.02	0.8
Emergency surgery				1.6	0.6-4.2	0.3
Procedure duration (per h)				1.1	1.05-1.24	<0.001
Fluid balance (per 1000 ml)				1.004	0.9-1	0.12
FFP transfusion				1.1	0.6-2.0	0.8
Platelet transfusion				2	1.04-3.7	0.04

OR: Odds Ratio | CI: Confidence Interval | eGFR: estimated Glomerular Filtration Rate | FFP: Fresh Frozen Plasma

4. Aims

The research that constitutes this PhD thesis had three general aims:

1) To study perioperative risk factors for mortality (incidence and predictors) after VS.

2) To study perioperative risk factors for adverse outcomes, namely, major cardiac events and acute kidney injury after VS.

3) To compare the accuracy and discriminative power of existing risk scores to predict mortality or adverse outcomes after VS.

These aims have the following distribution among the published papers:

1) Perioperative mortality was studied in papers A, B and D.

2) Perioperative adverse outcomes were studied in papers A and C.

3) Our results were compared with existing models in all papers. In papers B, C and D, we compared the accuracy and discriminative power of different risk scores. In papers C and D, we created a simple, objective, accurate model with the collected data.

5. Study designs, outcomes and statistical analysis

Each paper contains a detailed methods section. The first three studies have a retrospective design but the database used for papers B and C was registered prospectively. The knowledge acquired during the analysis of the initial studies was useful in designing the prospective study.

In papers A and B, we studied the in-hospital mortality. In the prospective paper D, the outcome was the 30-day mortality. We defined acute MI as an increase in high-sensitivity troponin levels > 0.034 ng/mL in the first 72h after surgery, following the ESC/American College of Cardiology criteria.[61] In paper C, we used MACE as described by Lee: stroke, ventricular fibrillation/cardiac arrest, complete heart block, cardiogenic pulmonary edema (CPE), acute heart failure (AHF), acute MI or cardiac death.[5] We defined AKI with KDIGO/AKIN criteria.[50,51]

In papers A to C, we used logistic regression to study independent predictors. In paper D, we used Cox-regression that accounts for time-to-event. In papers C and D, we created a model using the adjusted Odds Ratio (OR) of the independent variables as scoring points and analyzed the area under the receiver operating characteristic curve (AUROC) of the different risk indexes to measure their predictive discrimination. We used the Hosmer-Lemeshow test to determine the goodness of fit of our model (calibration), $p > .05$ for no significant difference between predictive model and observed data. To reduce the potential of overfitting, we selected the leave-one-out cross-validation approach and the bootstrapping method. We performed Bonferroni correction for multiple comparisons.

6. Publications

The results of this PhD thesis are the following publications:

A) Pedro Videira Reis, Mariana Morgado, Ines Valdoleiros, Marina Dias Neto, Joana Mourao. Complications of Endovascular Aneurysm Repair: Mortality, Myocardial Infarction and Acute Kidney Injury. Turkish Journal of Anaesthesioly and Reanimation 2018;46:222-8

B) Pedro Videira Reis, Ana Isabel Lopes, Diana Leite, João Moreira, Leonor Mendes, Sofia Ferraz, Tânia Amaral, Fernando Abelha. Predicting mortality in patients admitted to the Intensive Care Unit after open Vascular Surgery. Surgery Today 2019;49(10):836-842

C) Pedro Videira Reis, Ana Isabel Lopes, Diana Leite, João Moreira, Leonor Mendes, Sofia Ferraz, Tânia Amaral, Joana Mourão, Fernando Abelha. Major Cardiac Events in Patients Admitted to Intensive Care After Vascular Noncardiac Surgery: A Retrospective Cohort. Seminars in Cardiothoracic and Vascular Anesthesia 2019;23(3):293-299

D) Pedro Reis, Ana Isabel Lopes, Diana Leite, João Moreira, Leonor Mendes, Sofia Ferraz, Tânia Amaral, Fernando Abelha. Incidence, predictors and validation of risk scores to predict postoperative mortality after noncardiac vascular surgery, a prospective cohort study. International Journal of Surgery 2020;73:89-93

Paper A

Turk J Anaesthesiol Reanim 2018; 46: 222-8 DOI: 10.5152/TJAR.2018.37929

Original Article / Özgün Araştırma

Complications of Endovascular Aneurysm Repair: Mortality, Myocardial Infarction and Acute Kidney Injury

Endovasküler Anevrizma Onarımının Komplikasyonları: Mortalite, Miyokard İnfarktüsü ve Akut Böbrek Hasarı

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Cite this article as: Reis PV, Morgado M, Valdoleiros I, Dias Neto M, Mourão J. Complications of Endovascular Aneurysm Repair: Mortality, Myocardial Infarction and Acute Kidney Injury. Turk J Anaesthesiol Reanim 2018; 46: 222-8.

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Abstract / Öz

Objective: Patients undergoing endovascular aneurysm repair (EVAR) have comorbidities that increase the risk of death, myocardial infarction (MI) and acute kidney injury (AKI). Our aim was to evaluate the incidence and predictors of mortality, MI and AKI after EVAR and to compare AKI incidence with Vascular Surgery Kidney Injury Predictive Score (VSKIPS).

Methods: We conducted a retrospective study of EVAR procedures performed between March 2006 and November 2013. We defined mortality at 30 days, MI as an increase in troponin level to >0.034 ng mL^{-1} in the first 72 h and AKI as an increase in creatinine level to >0.3 mg dL^{-1} in the first 48 h after surgery. Risk factors were analysed using logistic regression calculating Hosmer–Lemeshow test and the area under the receiver operating curve (AUROC).

Results: Ninety-eight patients were included in the study. The incidence of mortality, MI, and AKI was 2%, 5%, and 18%, respectively. AKI increased the risk of MI [odds ratio (OR) 24.4, p=0.006]. Preoperative serum urea level of >50 mg dL^{-1} (OR 4.97, p=0.038), general anaesthesia (OR 9.64, p=0.002) and surgery duration (OR 1.53, p=0.043) were considered independent predictors of AKI. The AUROC of the AKI model was 0.886 compared with 0.793 of VSKIPS.

Conclusion: We found the incidence of mortality, MI and AKI consistent with that of previous studies. However, we may be underestimating the last two because of the short follow-up time. AKI was an independent predictor of MI. Preoperative serum urea level of >50 mg dL^{-1}, general anaesthesia and surgery duration were considered independent predictors of AKI.

Keywords: Abdominal aortic aneurysm, endovascular procedures, anaesthesia, myocardial infarction, mortality, acute kidney injury

Amaç: Endovasküler anevrizma onarımı (EVAR) uygulanan hastalarda ölüm, miyokard enfarktüsü (MI) ve akut böbrek hasarı (AKI) riskini artıran komorbiditeler vardır. Amacımız EVAR sonrası mortalite, MI ve AKI insidansını ve prediktörlerini değerlendirmek ve AKI insidansını Vasküler Cerrahi Böbrek Hasarı Öngörü Skoru (VSKIPS) ile karşılaştırmaktı.

Yöntemler: Mart 2006 ile Kasım 2013 tarihleri arasında gerçekleştirilen EVAR prosedürlerine ilişkin retrospektif bir çalışma gerçekleştirdik. 30 günde mortalite tanımlandı. MI, ilk 72 saatte troponin seviyesinde >0,034 ng mL^{-1} değerine varan artış olarak ve AKI ise ameliyat sonrası ilk 48 saatte kreatin seviyesinde >0,3 mg dL^{-1} değerine ulaşan artış olarak tanımlandı. Risk faktörleri, lojistik regresyonu hesaplayan Hosmer-Lemeshow test ve alıcı işlem eğrisi altındaki alan (AİEAA) kullanılarak analiz edildi.

Bulgular: Doksan sekiz hasta çalışmaya dahil edildi. Mortalite, MI ve AKI insidansı sırasıyla %2, %5 ve %18 idi. AKI, MI [odds ratio (OR) 24,4, p=0,006] riskini artırdı. Preoperatif >50 mg dL^{-1} (OR 4,97, p=0,038) serum üre düzeyi, genel anestezi (OR 9,64, p=0,002) ve ameliyat süresi (OR 1,53, p=0,043) AKI'nın bağımsız prediktörleri olarak kabul edildi. AKI modelinin AİEAA değeri 0,886 ve VSKIPS ise 0,793 idi.

Sonuç: Mortalite, MI ve AKI insidansını önceki çalışmalarla uyumlu bulduk. Ancak kısa takip süresi nedeniyle son ikisini yeterli seviyede değerlendirememiş olabiliriz. AKI, MI'nın bağımsız bir prediktörü idi. Preoperatif >50 mg dL^{-1} serum üre düzeyi, genel anestezi ve ameliyat süresi AKI'nın bağımsız prediktörleri olarak kabul edildi.

Anahtar Kelimeler: Abdominal aort anevrizması, endovasküler prosedürler, anestezi, miyokard infarktüsü, mortalite, akut böbrek hasarı

Introduction

Abdominal aortic aneurysms (AAAs) are arterial dilatations or widening of the abdominal aorta with a diameter of ≥3 cm in either anteroposterior or transverse planes (1-3). AAA accounts for 65% of aortic aneurysms and 90% of them are infrarenal (1).

Endovascular aneurysm repair (EVAR) of AAAs was first described in 1991 by Parodi and was designed as a less invasive approach than open surgical repair (OSR), without aortic clamping. EVAR aimed to reduce morbidity and mortality and promote haemodynamic stability. Studies have shown improvements in perioperative complications such as acute myocar-

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Received / Geliş Tarihi : 27.08.2017
Accepted / Kabul Tarihi : 06.02.2018

dial infarction (MI), acute kidney injury (AKI), mesenteric ischaemia and pneumonia (4, 5). It has become the first-line treatment for many patients and has enabled aneurysm repair in some patients considered unfit for OSR, such as older patients with severe comorbidities. Therefore, perioperative cardiac events should not be disregarded (4, 5). According to the European Society of Cardiology (ESC)/European Society of Anaesthesiology (ESA) guidelines, EVAR is an intermediate cardiac risk procedure, with a 1%-5% incidence of cardiac events (MI or cardiac death) (6). The 30-day mortality after EVAR has been shown to be significantly lower than that after OSR; however, the difference was mitigated when considering medium- and long-term mortality (2).

Acute kidney injury is a known complication after EVAR, independently increasing medium-term morbidity and mortality (7). Its incidence after EVAR is as high as 20% in some studies (7). Although EVAR would attenuate the perioperative renal injury associated with OSR, studies have shown that in the long term, renal function deteriorates more quickly after EVAR than after OSR (8). The aetiology of AKI after EVAR is probably multifactorial and several mechanisms may be involved, other than the repeated renal contrast agent injury. Microembolisation into the renal vasculature, suprarenal bare stent fixation with the risk of renal artery trauma, accessory renal artery occlusion and inflammatory and ischaemic response after endovascular manipulation have been suggested to play a part (3, 7, 9).

In 2015, Kashani et al. (10) presented a risk prediction model for AKI in patients undergoing vascular surgery. Two clinical multivariate models for the Vascular Surgery Kidney Injury Predictive Score (VSKIPS) were developed. Model 1 was restricted to perioperative variables (preoperative glomerular filtration rate, history of previous vascular intervention and preoperative exposure to diuretics or beta-blockers), whereas model 2 included all the above and also age and intraoperative variables [duration of the procedure, fluid balance, fresh-frozen plasma (FFP) and platelet transfusion]. Both models had a fair performance predicting the occurrence of postoperative AKI after major open vascular surgery of the descending thoracic or abdominal aorta (10).

Anaesthetic technique for EVAR procedures may include general anaesthesia (GA), regional anaesthesia (RA) (subarachnoid block, epidural block and combined spinal and epidural anaesthesia) and combined general and regional anaesthesia or local anaesthesia (LA) with or without sedation. There is some evidence suggesting that patients receiving LA or RA show fewer systemic complications (cardiac, renal and respiratory), lower hospital and intensive care unit (ICU) length of stay (LOS), as well as an improvement in 30-day mortality compared with those receiving GA (4, 5, 11, 12). However, there is still controversy regarding recommended anaesthetic technique for EVAR procedures being the choice made according to the patient's comorbidities, anaesthesiologist's preference and surgical requirements (4, 5, 11-13).

The aim of this study was to evaluate the incidence and predictors of mortality, MI and AKI after EVAR and to compare it with VSKIPS models.

Methods

After receiving approval from the institutional ethics committee, we performed a retrospective study including all adult patients undergoing EVAR between March 2006 and November 2013 at a university hospital. We collected the following data: demographic characteristics, American Society of Anaesthesiology (ASA) status classification, previous medical history, usual medication, pre- and postoperative analytic study, type of anaesthesia, intraoperative monitoring, anaesthesia and procedure duration, intra- or postoperative blood transfusions during hospital stay, aneurysm characteristics, type of endovascular stent graft, ICU and hospital LOS, incidence of MI (defined as an increase in troponin level to >0.034 ng mL^{-1} in the first 72 h after surgery), occurrence of AKI (defined as an increase in creatinine level to >0.3 mg dL^{-1} in the first 48 h after surgery, according to the KDIGO classification) (14) and 30-day mortality. For the AKI analysis, we excluded patients with preoperative chronic renal failure.

Statistical analysis

Statistical analysis was performed using the IBM Statistical Package for the Social Sciences software for Windows version 22.0 (IBM SPSS Statistics; Armonk, NY, USA). Descriptive analysis, independent t, Mann-Whitney U, Fisher and chi-square tests were performed. Since we analysed three outcomes (mortality, MI and AKI), we used Bonferroni correction to decrease the probability of a type I error, which resulted in a p value of <0.017 being statistically significant. Univariate and multivariate logistic regressions were used to calculate the odds ratio (OR) and its 95% confidence interval (CI). In the multivariate logistic regression, we used the forward method including all variables with $p<0.05$ to identify the independent predictors of the outcomes. The Hosmer-Lemeshow test for the goodness-of-fit and the area under the receiver operating curve (AUROC) to measure the predictive discrimination of the model were also analysed.

Results

Patient characteristics are presented in Table 1. The majority (98%) of the aneurysms were infrarenal, and approximately half of them (52%) involved the iliac arteries. Pre-operatively, 56 patients were medicated with antiplatelet therapy, 45 in monotherapy and 11 with dual therapy. Postoperatively, 72 patients required antiplatelet therapy (41 aspirin, 24 clopidogrel, 1 ticlopidine, 6 aspirin plus clopidogrel) and 17 patients started anticoagulants after surgery.

Table 2 summarises the procedure and postoperative variables. Of the 79 RAs performed, 5 were subarachnoid blocks, 33 epidural blocks and 41 combined spinal and epidural blocks. The three combined anaesthesia were GA with epidural block. During the procedure, all patients had ASA

Table 1. Summary of patients' characteristics

	n=98
Sex	
Male	93 (95)
Female	5 (5)
Age, years	75.0±6.8
ASA physical status	
II	29 (30)
III	57 (58)
IV	10 (10)
V	2 (2)
Comorbidities	
Arterial hypertension	88 (90)
Dyslipidaemia	66 (68)
Coronary disease	40 (41)
Cardiac arrhythmia	27 (28)
Obesity	26 (27)
CHF	24 (25)
COPD	23 (24)
DM	20 (21)
CVD	12 (12)
CRF	11 (11)
PAOD	9 (9)
Usual medication	
Statin	58 (73)
Diuretic	35 (44)
β-blocker	31 (39)
Antiplatelet therapy	56 (69)
Anticoagulation therapy	9 (11)
Digoxin	2 (3)
Aneurysm characteristics	
Diameter (cm)	6.1 [5.4–7.0]
Length (cm)	5.5 [5.0–7.0]
Iliac artery involvement	44 (52)
Renal artery involvement	2 (2)
Preoperative analytic study	
Haemoglobin (g dL^{-1})	13.3±1.9
Haematocrit (%)	40.4 [36.5–43.6]
Platelets (109/L)	182.0 [154.0–218.8]
Creatinine (mg dL^{-1})	1.2 [1.0–1.5]
Urea (mg dL^{-1})	49.0 [38.0–61.0]

N (%), mean ± SD: standard deviation or median; IQR: interquartile range [P25–P75]; ASA: American Society of Anaesthesiology; HBP: high blood pressure; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; CVD: cerebrovascular disease; CRF: chronic renal failure; PAOD: peripheral arterial occlusive disease.

Table 2. Intra- and postoperative variables

	n=98
Type of anaesthesia	
BGA	17 (18)
RA	79 (81)
Combined anaesthesia (GA+RA)	3 (3)
Sedation/local anaesthesia	1 (1)
Type of endovascular stent graft	
Zenith cook	68 (80)
Endurant medtronic	10 (12)
Others	7 (8)
Anaesthesia duration, hours	5.0 [4.0–6.0]
Surgery duration, hours	4.0 [3.0–4.5]
RBC transfusion	26 (27)
Postoperative destination	
ICU	73 (77)
Intermediate care unit	2 (2)
Hospital ward	19 (20)
Postoperative analytic study	
Haemoglobin (g dL^{-1})	11.1±1.5
Haemoglobin min (g dL^{-1})	10.0±1.7
Haematocrit (%)	33.3±4.4
Haematocrit min (%)	30.3±5.1
Platelets (10^9/L)	135.0 [112.0–155.5]
Platelets min (10^9/L)	124.0 [103.5–146.0]
Creatinine (mg dL^{-1})	1.0 [0.8–1.2]
Creatinine max (mg dL^{-1})	1.2 [1.0-1.6]
Urea (mg dL^{-1})	34.0 [26.0-43.5]
Length of ICU stay, days	1 [1-2]
Length of hospital stay, days	5 [4-7]
Postoperative complications	
Stroke	1 (1)
MI	5 (5)
AKI	15 (15)
Acute pulmonary oedema	1 (1)
Death	2 (2)

N (%), mean ± SD: standard deviation or median; IQR: interquartile range [P25-P75]; BGA: balanced general anaesthesia; RA: regional anaesthesia; GA: general anaesthesia; RBC: red blood cells; ICU: intensive care unit; min: minimum; max: maximum; MI: myocardial infarction; AKI: acute kidney injury

standard monitoring and 59 of them had invasive blood pressure monitoring. Red blood cell (RBC) transfusion was given intraoperatively in 26 patients. One patient received two units of platelets, and another patient received five units of FFP. Postoperatively, nine patients received RBC transfusion during hospital stay.

Table 3. Perioperative variables according to AKI occurrence

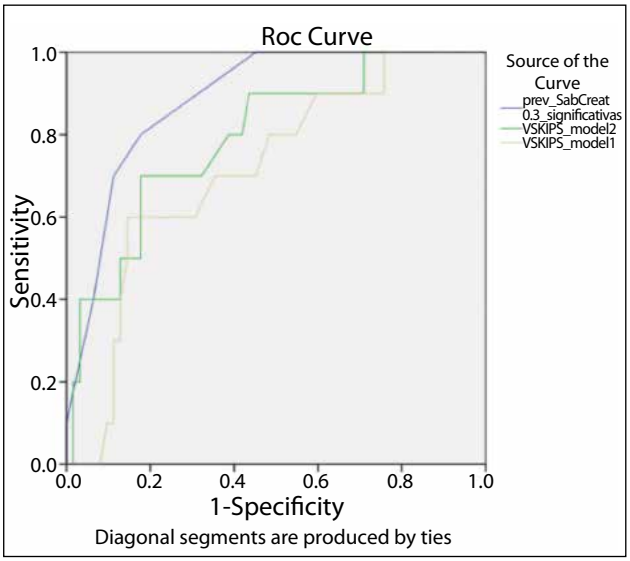
	No AKI (n=68)	AKI (n=15)	p
Male sex[1]	64 (94)	15 (100)	0.339[a]
Age[2]	74.2±6.9	78.0±5.6	0.097[b]
ASA physical status II/III[1]	59 (87)	13 (87)	1.0[a]
ASA physical status IV/V[1]	9 (13)	2 (13)	
HBP[1]	62 (91)	14 (93)	1.0[a]
Dyslipidaemia[1]	48 (68)	8 (53)	0.197[a]
Coronary Heart Disease[1]	28 (41)	7 (47)	0.697[a]
Obesity[1]	21 (31)	5 (33)	1.0[a]
COPD[1]	18 (26)	4 (27)	1.0[a]
CHF[1]	17 (25)	6 (40)	0.240[a]
DM[1]	15 (22)	5 (33)	0.341[a]
CVD[1]	8 (12)	2 (13)	1.0[a]
CRF[1]	8 (12)	3 (20)	0.409[a]
PAOD[1]	4 (6)	2 (13)	0.296[a]
Diuretic medication[1]	25 (37)	7 (47)	0.476[a]
β-blocker medication[1]	22 (32)	4 (27)	0.767[a]
Statin medication[1]	42 (62)	8 (53)	0.546[a]
Anticoagulation medication[1]	5 (7)	4 (27)	0.029[a]
ACEI/ARA medication[1]	28 (41)	4 (27)	0.386[a]
NSAID medication[2]	15 (19)	0 (0)	1.0[a]
Aneurysm diameter (mm)[3]	60 [53–70]	68 [64–82]	0.023[c]
Preoperative haemoglobin (g dL^{-1})[2]	13.5±1.9	12.6±2.1	0.273[b]
Preoperative haemoglobin <10 g dL^{-11}	2 (3)	3 (20)	0.049[a]
Preoperative creatinine (mg dL^{-1})[3]	1.15 [0.96–1.41]	1.40 [1.20–1.87]	0.005[c]
Preoperative creatinine >1.2 mg dL^{-11}	25 (37)	11 (73)	0.010[a]
Preoperative urea (mg dL^{-1})[3]	46 [38–59]	57 [52–79]	0.003[c]
Preoperative urea >50 mg dL^{-11}	24 (36)	12 (80)	0.003[a]
General anaesthesia[1]	8 (12)	8 (53)	0.001[a]
Regional anaesthesia[1]	59 (87)	6 (40)	0.001[a]
Surgery duration (hours)[3]	4.0 [3.0–4.5]	4.0 [4.0–6.1]	0.057[c]
Intraoperative RBC transfusion[1]	18 (26)	6 (40)	0.350[a]
Postoperative haemoglobin (g dL^{-1})[2]	10.2±1.6	8.4±0.9	<0.001[b]
Postoperative haemoglobin <10 g dL^{-12}	26 (38)	14 (93)	<0.001[a]
Postoperative RBC transfusion[2]	3 (4)	4 (27)	0.018[a]
Myocardial infarction	1 (1)	4 (27)	0.003[a]
Lenth of stay (days)[3]	4.5 [4.0–6.0]	12.0 [6.0–19.0]	<0.001[c]
Hospital mortality[2]	0 (0)	2 (13)	0.031[a]

[1]N (%), [2]mean ± standard deviation, [3]median and interquartile range [P25-P75].
[a]Fisher or Qui-square test, [b]Student t test, [c]Mann–Whitney U test. AKI: acute kidney injury; ASA: American Society of Anaesthesiology; HBP: high blood pressure; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; CVD: cerebrovascular disease; CRF: chronic renal failure; PAOD: peripheral arterial occlusive disease; ACEI/ARA: angiotensin converting enzyme inhibitor/receptor antagonist; RBC: red blood cells

Table 4. Univariate and multivariate analyses of AKI

	Simple OR [95% CI]	p	Adjusted OR [95% CI]	p
Preoperative anticoagulant medication	4.58 [1.06–19.78]	0.041	-	-
Preoperative haemoglobin <10 g dL^{-1}	8.25 [1.24–54.72]	0.029	-	-
Preoperative creatinine >1.2 mg dL^{-1}	7.43 [1.36–16.44]	0.015	-	-
Preoperative urea >50 mg dL^{-1}	7.17 [1.84–27.93]	0.005	4.97 [1.10–22.52]	0.038
General anaesthesia	8.57 [2.45–30.05]	0.001	9.64 [2.26–41.12]	0.002
Surgery duration (hours)	1.48 [1.05–2.09]	0.027	1.53 [1.01–2.32]	0.043
Postoperative haemoglobin (g dL^{-1})	0.423 [0.26–0.69]	0.001	-	-
Postoperative RBC transfusion	7.88 [1.55–40.12]	0.013	-	-
Perioperative myocardial infarction	24.36 [2.49–238.72]	0.006	-	-

AKI: acute kidney injury; RBC: red blood cells



Score	AUROC	Hosmer–Lemeshow
VSKIPS model 1	0.715	-
VSKIPS model 2	0.793	-
Study predictors	0.886	0.239

Figure 1. Acute kidney injury prediction
AUROC: area under the receiver operating curve; VSKIPS: vascular surgery kidney injury predictive score

The incidence of 30-day mortality was 2% (2 of 98). Patients who died had higher ASA physical status (p=0.011), were more frequently under anticoagulation medication pre-operatively (p=0.008) and had lower preoperative haemoglobin (9.2±0.6 vs. 13.4±1.8, p=0.002).

The incidence of MI was 5% (5 of 98). Pre- and intraoperative variables were similar between the two groups. Patients having MI had higher postoperative creatinine level [2.3 (1.9-6.1) vs. 1.1 (0.9-1.5), p=0.002]. After multivariate analysis, only postoperative AKI was identified as an independent predictor of MI (adjusted OR 24.4, 95% CI, 2.5-238.7; p=0.006).

The incidence of AKI was 18% (15 of 83). Table 3 displays the perioperative data according to the occurrence of AKI. Patient characteristics were similar between the two groups. Univariate and multivariate logistic regression can be seen in Table 4. Preoperative serum urea level of >50 mg dL^{-1} (OR 4.97, p=0.038), GA (OR 9.64, p=0.002) and surgery duration (OR 1.53, p=0.043) were considered independent predictors of AKI in multivariate analysis. Hosmer-Lemeshow test value was 0.239 and AUROC was 0.886, whereas VSKIPS was 0.793 (Figure 1). Patients with AKI had higher hospital LOS [5 (4-6) vs. 12 (6-19) days, p<0.001].

Discussion

In our study, the 30-day mortality after EVAR was 2%. There are two meta-analyses comparing EVAR with OSR. In the meta-analysis conducted by Stather et al. (15) the 30-day mortality rate was found to be 1.4%. The difference in mortality may be because our patients were older, patients had a higher ASA classification or our study included only elective EVAR of Randomized Controlled Trials. Thomas et al. (16) performed a meta-analysis including observational studies and concluded that global 30-day mortality of EVAR was 4.2% but decreased to 1.4% if only elective cases were considered. Egorova et al. (13) elaborated a perioperative risk scoring system based on the predictors of 30-day mortality: renal failure, lower extremity ischaemia, age of >75 years, liver disease, congestive heart failure, female sex, neurological condition, chronic pulmonary condition, surgeon EVAR experience of <3 cases and hospital annual volume of <7 cases. The performance of that risk score in our sample was poor (AUROC, 0.570) perhaps because of the sample size. Although many surgeons perform EVAR at our hospital, none has less than three cases of experience. During the first 2 years, hospital annual volume was around 7 cases, but since

2008, there have been 12-18 cases per year. The two cases of mortality were after 2009.

According to the European Society for Vascular Surgery, cardiac events are a major cause of morbidity and mortality after non-cardiac surgery causing 10%-40% of perioperative deaths (6). Despite the prevalence of cardiovascular risk factors in our population, we may say that none of our deaths was caused by MI.

The incidence of MI in our study was 5% in the first 72 h after surgery. The ESC/ESA guidelines on non-cardiac surgery predict 1%-5% of cardiac events (cardiac death and MI) until 30 days postoperatively (6). It is possible that we may be underestimating the occurrence of MI in our study because of the shorter follow-up time. The incidence of MI after elective EVAR in the meta-analysis presented by Stather et al. (15) was 6.8% similar to 6.3% found in the meta-analysis of Thomas et al. (16) but neither specified the follow-up time for this parameter.

The ESC/ESA guidelines linked chronic renal disease with increased risk of cardiovascular disease, it being an independent risk factor for adverse postoperative cardiovascular outcomes, including MI, stroke and progression of heart failure (6). In our study, postoperative AKI was an independent predictor of MI. In a 2015 prospective cohort study, AKI (defined according to the KDIGO classification) predicted the risk of chronic non-fatal MI in patients with type 2 diabetes (17). However, this study did not define the cause of AKI and was restricted to diabetic patients. The reasons why AKI can predict MI are unknown; one possible explanation is the systemic inflammation, but it is possible that AKI constitutes a marker of renal and overall frailty (17).

The incidence of AKI was 18% in our study, which is consistent with that of previous studies (19%-29%) (7, 18). Incidence may vary across studies for various reasons, one of them being the difference in classification of AKI.

We found that GA and surgery duration increased the risk of AKI. In a study using the multicentre EUROSTAR registry (EUROpean collaborators on Stent graft Techniques for AAA Repair), (19) there were fewer systemic complications (cardiac, pulmonary, renal and sepsis) for LA with sedation than for GA (6.6% vs. 13.0%, p=0.0015) and for RA than for GA (9.5% vs. 13%, p=0.0007). There is a potential bias that patients undergoing GA had more complex procedures (p=0.011), more additional procedures (p<0.001) and longer procedure duration (p<0.001), and that could be the case in our study (19). Additionally, longer procedures could mean more contrast that may contribute to the postoperative AKI.

Preoperative urea level of >50 mg dL^{-1} increased the risk of postoperative AKI. This finding may indicate the need to optimise renal function and euvolemia pre-operatively, avoid nephrotoxic drugs, carefully watch the amount of contrast administered and perform contrast nephropathy prophylaxis whenever indicated. This outcome may open future perspectives as a possible predictor of complications.

We compared our findings with the VSKIPS models (model 1: AUROC, 0.715 and model 2: AUROC, 0.793) (10). Our study had several variables in common with VSKIPS (age, preoperative exposure to diuretics and beta-blockers, duration of the procedure and plasma and platelet transfusion), but we did not use history of previous vascular intervention or fluid balance as we did not have that information available in our data. Our findings were concordant with this previous study, as model 2 performed better than model 1 (AUROC, 0.715 and 0.793, respectively). However, VSKIPS defined AKI with the Acute Kidney Injury Network criteria (using serum creatinine levels and hourly urine output), whereas our study was based on the KDIGO classification (defined as an increase in creatinine level to >0.3 mg dL^{-1} in the first 48 h after surgery) (14).

According to the European Society of Intensive Care Medicine (ESICM), the ICU and hospital LOSs are important for health finance evaluations but not as indicators of clinical outcome because they depend on hospital and healthcare policy as well as on physician performance (14). Better planning to avoid AKI may influence both hospital and ICU LOS.

Study limitations

It was impossible to collect any information regarding the amount of contrast or AKI preventive strategies used during the procedure. We cannot exclude the possibility that a part of the documented AKI may be related to contrast-induced nephropathy. We do not have available information regarding the need for renal replacement therapy. Another limitation is that we only evaluated the short-term mortality. According to the ESA/ESICM, (14) the mortality should be reported until 90 days and preferably 1 year after surgery, although short-term mortality may remain relevant as a treatment safety outcome. We did not register surgery-related complications, including the presence of endoleak, aneurysm rupture or conversion to OSR, and the technical difficulties or success rates of the intervention were not taken into account.

Conclusion

We found the incidence of mortality, MI and AKI consistent with that of previous studies. Preoperative serum urea level of >50 mg dL^{-1}, GA and surgery duration were considered independent predictors of AKI. AKI was an independent predictor of MI. The VSKIPS models developed for major open vascular surgery showed a fair performance for EVAR patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Centro Hospitalar São João (CES 76-14; 13.03.2014).

Informed Consent: Ethics committee did not require written informed consent for a retrospective study since data was analysed without patient identification.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - P.V.R., J.M.; Design - P.V.R., J.M.; Supervision - J.M.; Resources - M.D.N.; Materials - M.D.N.; Data Collection and/or Processing - P.V.R., M.M., I.V.; Analysis and/or Interpretation - P.V.R., M.M., I.V., J.M.; Literature Search - P.V.R., M.M., I.V.; Writing Manuscript - P.V.R., M.M., I.V; Critical Review - M.D.N., J.M.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Etik Komite Onayı: Bu çalışma için etik kurul onayı Centro Hospitalar São João (CES 76-14; 13.03.2014) Etik Kurulu'ndan alınmıştır.

Hasta Onamı: Retrospektif çalışma hastanın kimlik bilgileri olmadan yapıldığından, Etik komite yazılı bilgilendirilmiş onam talep etmemiştir.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir - P.V.R., J.M.; Tasarım - P.V.R., J.M.; Denetleme - J.M.; Kaynaklar - M.D.N.; Malzemeler - M.D.N.; Veri Toplanması ve/veya İşlemesi - P.V.R., M.M., I.V.; Analiz ve/veya Yorum - P.V.R., M.M., I.V., J.M.; Literatür Taraması - P.V.R., M.M., I.V.; Yazıyı Yazan - P.V.R., M.M., I.V; Eleştirel İnceleme - M.D.N., J.M.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

References

1. Lorentz MN, Boni CL, Soares RR. Anesthesia for endovascular surgery of the abdominal aorta. Rev Bras Anestesiol 2008; 58: 525-32. [CrossRef]
2. Paravastu SC, Jayarajasingam R, Cottam R, Palfreyman SJ, Michaels JA, Thomas SM. Endovascular repair of abdominal aortic aneurysm. Cochrane Database Syst Rev 2014; 23: CD004178.
3. Moll FL, Powell JT, Fraedrich G, Verzini F, Haulon S, Waltham M, et al. Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. Eur J Vasc Endovasc Surg 2011; 41(Suppl 1): S1-58.
4. Elisha S, Nagelhout J, Heiner J, Gabot M. Anesthesia case management for endovascular aortic aneurysm repair. AANA J 2014; 82: 145-52.
5. Wylie SJ, Wong GT, Chan YC, Irwin MG. Endovascular aneurysm repair: a perioperative perspective. Acta Anaesthesiol Scand 2012; 56: 941-9. [CrossRef]
6. Kristensen SD, Knuuti J, Saraste A, Anker S, Botker HE, De Hert S, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management. Kardiol Pol 2014; 72: 857-918. [CrossRef]
7. Saratzis A, Melas N, Mahmood A, Sarafidis P. Incidence of Acute Kidney Injury (AKI) after Endovascular Abdominal Aortic Aneurysm Repair (EVAR) and Impact on Outcome. Eur J Vasc Endovasc Surg 2015; 49: 534-40. [CrossRef]
8. Mills JL, Sr., Duong ST, Leon LR, Jr., Goshima KR, Ihnat DM, Wendel CS, et al. Comparison of the effects of open and endovascular aortic aneurysm repair on long-term renal function using chronic kidney disease staging based on glomerular filtration rate. J Vasc Surg 2008; 47: 1141-9. [CrossRef]
9. Saratzis AN, Goodyear S, Sur H, Saedon M, Imray C, Mahmood A. Acute kidney injury after endovascular repair of abdominal aortic aneurysm. J Endovasc Ther 2013; 20: 315-30. [CrossRef]
10. Kashani K, Steuernagle JHT, Akhoundi A, Alsara A, Hanson AC, Kor DJ. Vascular Surgery Kidney Injury Predictive Score: A Historical Cohort Study. J Cardiothorac Vasc Anesth 2015; 29: 1588-95. [CrossRef]
11. Franz R, Hartman J, Wright M. Comparison of anesthesia technique on outcomes of endovascular repair of abdominal aortic aneurysms: a five-year review of monitored anesthesia care with local anesthesia vs. general or regional anesthesia. J Cardiovasc Surg (Torino) 2011; 52: 567-77.
12. Smaka TJ, Cobas M, Velazquez OC, Lubarsky DA. Perioperative management of endovascular abdominal aortic aneurysm repair: update 2010. J Cardiothorac Vasc Anesth 2011; 25: 166-76. [CrossRef]
13. Egorova N, Giacovelli JK, Gelijns A, Mureebe L, Greco G, Morrissey N, et al. Defining high-risk patients for endovascular aneurysm repair. J Vasc Surg 2009; 50: 1271-9. [CrossRef]
14. Jammer I, Wickboldt N, Sander M, Smith A, Schultz MJ, Pelosi P, et al. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: a statement from the ESA-ESICM joint taskforce on perioperative outcome measures. Eur J Anaesthesiol 2015; 32: 88-105. [CrossRef]
15. Stather PW, Sidloff D, Dattani N, Choke E, Bown MJ, Sayers RD. Systematic review and meta-analysis of the early and late outcomes of open and endovascular repair of abdominal aortic aneurysm. Br J Surg 2013; 100: 863-72. [CrossRef]
16. Thomas DM, Hulten EA, Ellis ST, Anderson DM, Anderson N, McRae F, et al. Open versus Endovascular Repair of Abdominal Aortic Aneurysm in the Elective and Emergent Setting in a Pooled Population of 37,781 Patients: A Systematic Review and Meta-Analysis. ISRN Cardiol 2014: 149243.
17. Monseu M, Gand E, Saulnier PJ, Ragot S, Piguel X, Zaoui P, et al. Acute Kidney Injury Predicts Major Adverse Outcomes in Diabetes: Synergic Impact With Low Glomerular Filtration Rate and Albuminuria. Diabetes Care 2015; 38: 2333-40. [CrossRef]
18. Sailer AM, Nelemans PJ, van Berlo C, Yazar O, de Haan MW, Fleischmann D, et al. Endovascular treatment of complex aortic aneurysms: prevalence of acute kidney injury and effect on long-term renal function. Eur Radiol 2016; 26: 1613-9. [CrossRef]
19. Ruppert V, Leurs LJ, Steckmeier B, Buth J, Umscheid T. Influence of anesthesia type on outcome after endovascular aortic aneurysm repair: an analysis based on EUROSTAR data. J Vasc Surg 2006; 44: 16-21. [CrossRef]

Paper B

Surgery Today
https://doi.org/10.1007/s00595-019-01805-w

ORIGINAL ARTICLE

Predicting mortality in patients admitted to the intensive care unit after open vascular surgery

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Received: 17 July 2018 / Accepted: 23 March 2019

Abstract

Purposes Vascular surgery (VS) has a higher perioperative mortality than other types of surgery. We compared different scores for predicting mortality in patients admitted to the intensive care unit (ICU) after open VS.

Methods Patients admitted to the ICU after open VS from 2006 to 2013 were included. We calculated the Acute Physiology and Chronic Health Evaluation (APACHE), Simplified Acute Physiology Score (SAPS), Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (POSSUM) and Preoperative Score to Predict Postoperative Mortality (POSPOM). We performed multivariate logistic regression to assess independent factors with the calculation of odds ratios (ORs) and 95% confidence intervals (CIs). We tested the predictive ability of the scores using the area under the receiver operating characteristics curve (AUROC).

Results A total of 833 consecutive patients were included. Hospital mortality was 5.1% (1.3% after intermediate-risk and 8.4% after high-risk surgery). In the multivariate analysis, the age (OR 1.04, 95% CI 1.01–1.08, $p=0.013$), smoking status (OR 2.46, 95% CI 1.16–5.21, $p=0.019$), surgery risk (OR 2.92, 95% CI 1.05–8.08, $p=0.040$), serum sodium level (OR 1.17, 95% CI 1.10–1.26, $p<0.001$), urea (OR 1.01, 95% CI 1.01–1.02, $p=0.001$) and leukocyte count (OR 1.05, 95% CI 1.01–1.10, $p=0.009$) at admission were considered independent predictors. Hematocrit (0.86, 95% CI 0.80–0.93, $p<0.001$) was considered an independent protective factor. The AUROC of our model was 0.860, compared to SAPS (0.752), APACHE (0.774), POSPOM (0.798) and POSSUM (0.829).

Conclusion The observed mortality was within the predicted range (1–5% after intermediate-risk and > 5% after high-risk surgery). POSSUM and POSPOM had slightly better predictive capacity than SAPS or APACHE.

Keywords Hospital mortality · SAPS · APACHE · Intensive care unit · Vascular surgery

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Published online: 09 April 2019

Introduction

Vascular surgery (VS) accounts for 0.5–2% of the 234 million surgeries performed every year [1, 2]. Anesthetic and surgical techniques along with better planning and monitoring have decreased the intraoperative mortality [3]. However, postoperative mortality is still frequent, and 4% of patients die before hospital discharge while 5.5% die within a year [4, 5]. Deaths predominantly occur in older patients and those who undergo major or emergent surgery, who have severe coexisting diseases or who develop complications [6–9]. Perioperative complications may affect 12% of patients, a rate that tends to increase with age and comorbidities [7, 10, 11]. Immediate postoperative care allows for closer monitoring and early intervention to reduce complications and deaths [6, 7, 11]. High-risk patients or those who receive certain surgeries may benefit from admission to a surgical intensive care unit (SICU), but these beds have a limited capacity and are expensive to occupy [12, 13].

Risk models, such as the Simplified Acute Physiology Score (SAPS) and Acute Physiology and Chronic Health Evaluation (APACHE), were designed to predict mortality after ICU admission [14–16]. They focus on the severity of illness at admission, which may not be adequate for post-surgical patients [17]. The Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (POSSUM), with or without the Portsmouth (P-POSSUM) modification and its Vascular variant (V-POSSUM), has been used to predict the 30-day mortality and morbidity after VS, but they include pre- and intraoperative variables, which may preclude their use in preoperative planning and risk estimation [18, 19]. The Preoperative Score to Predict Postoperative Mortality (POSPOM) overcomes this problem but was derived using many types of surgery [20]. The National Surgical Quality Improvement Program (NSQIP) of the American College of Surgeons (ACS) has also developed a score for predicting the postoperative mortality that can be calculated online, including a subset for use in VS, but they did not publish the equation, making it unavailable for broad clinical research [21, 22]. Assessing the mortality risk is important in an era rife with concerns about variations in the quality of care and use of healthcare resources.

The aim of this study was to evaluate the determinants of hospital mortality (HM) in a cohort of patients admitted to the SICU after open VS. In addition, we compared our model with the ICU risk scores SAPS or APACHE and the surgical risk scores V-POSSUM or POSPOM for mortality prediction after VS.

Materials and methods

Study design, setting and participants

We conducted a retrospective cohort study including all patients admitted to the Surgical ICU after open VS from January 2006 to July 2013 in a large academic hospital. We defined exposures and outcomes and planned the analysis before looking at the data. The institutional ethics committee approved the protocol. This report complies with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational cohort studies [23].

Data collection

We prospectively collected the following variables at ICU admission: age, gender, medical history, type of admission (elective or emergent), type of surgery and ventilation. Surgeries were divided into intermediate risk (carotid endarterectomy and peripheral angioplasty) and high risk (open aortic surgery, lower limb revascularization, thromboembolectomy and amputation) according to the joint guidelines of European Society of Cardiology (ESC) and European Society of Anesthesiology (ESA) [24]. During the ICU stay, prospective records were collected, including data on the vital signs, laboratory results, major cardiovascular events (MACE) (stroke, acute myocardial infarction defined as a rise in troponin > 0.034 ng/ml in the first 72 h after surgery, de novo atrial fibrillation or heart failure including pulmonary edema, ventricular fibrillation or cardiac arrest, complete heart block), renal complications (acute kidney injury as defined by the Acute Kidney Injury Network criteria [25]), length of stay (LOS) and mortality. The ICU records at admission included the SAPS and APACHE scores, whereas the POSSUM and POSPOM were calculated in retrospective.

Statistical analyses

We used descriptive statistics to summarize the data. We performed the Kolmogorov–Smirnov test and a histogram analysis to assess the normality of data and selected parametric (independent sample *t* test) or non-parametric tests (Mann–Whitney *U* test) accordingly. To compare proportions between groups in the univariate analysis, we used the Chi square test. We determined independent predictors of MACE using multivariate logistic regression with the forward conditional method, calculating the odds ratios (OR) and 95% confidence intervals (CIs). We created a model using the adjusted OR of the independent variables

as scoring points and analyzed the area under the receiver operating characteristics curve (AUROC) of the different risk indexes to measure their predictive discrimination. We used the Hosmer–Lemeshow test to determine the goodness of fit of our model (calibration), with $p > 0.05$ taken to indicate no significant difference between the predictive model and observed data. To reduce the risk of overfitting, we selected the leave-one-out cross-validation approach and bootstrapping method ($n = 1000$ samples). We performed Bonferroni correction for multiple comparisons. We used Stata software, version 14 (StataCorp) and SPSS software, version 23 (IBM) to analyze the data.

Results

We admitted 833 patients to the SICU after open VS, most of them male (80%). The HM was 5.1% overall, 1.3% after intermediate-risk surgery ($n = 5/382$) and 8.4% ($n = 38/451$) after high-risk surgery. Table 1 presents the variable distribution by HM. Aortic surgery was more common than

Table 2 Mortality by surgical site according to the expected risk

Surgical risk	Surgical site	Mortality (%)
Intermediate	Carotid	0.8
	Lower limb	1.5
High-risk	Lower limb	7.1
	Aortic	8.3

Table 1 Results of the univariate analysis of hospital mortality

Variables	Survival group $n = 790$	Mortality group $n = 43$	p value
Male gender, *n* (%)	624 (79.0)	38 (88.4)	0.138*
Age (years), median [IQR]	69 [60–76]	73 [67–78]	**0.010**†
Prior medical history, *n* (%)			
Arterial hypertension	398 (50.4)	24 (55.8)	0.488*
Diabetes mellitus	183 (23.2)	13 (30.2)	0.287*
Current smoker	164 (20.8)	16 (37.2)	**0.011***
Peripheral arterial disease	236 (29.9)	19 (44.2)	**0.046***
Coronary disease	257 (32.5)	19 (44.2)	0.114*
Congestive heart failure	179 (22.7)	22 (51.2)	**< 0.001***
Cerebrovascular disease	367 (46.5)	12 (27.9)	**0.017***
Chronic kidney disease	67 (8.5)	11 (25.6)	**0.001***
Emergent surgery, *n* (%)	63 (8.0)	11 (25.6)	**< 0.001***
High-risk surgery, *n* (%)	413 (52.3)	38 (88.4)	**< 0.001***
At admission			
Mechanical ventilation, *n* (%)	170 (21.5)	19 (44.2)	**< 0.001***
Body temperature, median [IQR]	35.9 [34.9–36.1]	35.0 [34.3–36.0]	0.116†
Systolic pressure, median [IQR]	133 [110–158]	105 [78–144]	**< 0.001**†
Mean arterial pressure, median [IQR]	89 [74–100]	78 [57–97]	**0.011**†
Heart rate, median [IQR]	78 [65–89]	91 [78–116]	**< 0.001**†
Respiratory rate, median [IQR]	14 [12–16]	16 [14–16]	**0.010**†
Hematocrit, median [IQR]	33.0 [29.7–36.0]	29.0 [22.5–33.0]	**< 0.001**†
Serum urea, median [IQR]	32 [25–43]	50 [30–70]	**< 0.001**†
Serum creatinine, median [IQR]	0.9 [0.7–1.2]	1.3 [0.8–2.1]	**< 0.001**†
Serum potassium, median [IQR]	3.8 [3.5–4.1]	3.9 [3.5–4.6]	0.171†
Serum sodium, median [IQR]	139 [137–141]	144 [140–147]	**< 0.001**†
Leukocytes count, median [IQR]	10.4 [7.9–12.9]	13.4 [7.6–20.0]	**0.002**†
During stay			
Cardiovascular events, *n* (%)	38 (4.8)	16 (37.2)	**< 0.001***
Renal complications, *n* (%)	33 (4.3)	10 (23.3)	**< 0.001***
Length of stay (hours), median [IQR]	21 [17–43]	44 [18–68]	**0.001**†

IQR interquartile range [P25–P75]

* Chi square test, † Mann–Whitney test

lower limb surgery or carotid endarterectomy and had a significantly higher mortality (8.4% vs. 6.2% vs. 0.8%, respectively; $p < 0.001$). Table 2 shows the HM by surgical site according to the expected risk. Regarding the type of admission, elective surgery had an HM rate of 4.2%, whereas emergent surgery had a rate of 14.9%. The incidence of cardiovascular events was 6.5%, and that of renal complications was 6.8% during the SICU stay; both were associated with a higher HM ($p < 0.001$). Almost half (49%) of the HM incidents occurred during the SICU stay.

Table 3 shows the difference in mortality scores. All listed scores were significantly higher ($p < 0.001$) in the mortality group than in the survival group. POSSUM predicted an HM of 5.3% ($n = 44$) and observed/expected ratio of 0.98 (43/44). Table 4 shows the results of multiple logistic regression for assessing the effect of pre-admission and at-admission variables on HM. The age, smoking status, surgery risk, serum sodium level, urea and leukocyte count at admission were considered independent predictors. Hematocrit after surgery was considered an independent protective factor with a 14% adjusted risk reduction for each 1% increase in hematocrit.

Figure 1 graphically displays the AUROC of the different scores. Our model had an AUROC of 0.860 with a Hosmer–Lemeshow test for the goodness of fit of 0.90. The ICU scores SAPS (0.752) and APACHE (0.774) were slightly worse than the surgical risk scores POSPOM (0.798) and POSSUM (0.829). Using the leave-one-out cross-validation approach and the bootstrap analysis resulted in the same AUROC: 0.858.

Discussion

In this study, we assessed the incidence and possible predictors associated with HM following SICU admission after VS. The estimated mortality according to ESA guidelines is

Table 3 Intensive care and surgical risk scores by mortality

Risk scores	Survival group $n = 790$	Mortality group $n = 43$	p value
SAPS, median [IQR]	19 [13–25]	31 [16–46]	**< 0.001***
APACHE, median [IQR]	9 [7–12]	15 [11–21]	**< 0.001***
POSPOM, median [IQR]	14 [12–16]	18 [16–23]	**< 0.001***
V-POSSUM, median [IQR]	25 [21–29]	34 [29–40]	**< 0.001***

IQR interquartile range [P25–P75], *SAPS* Simplified Acute Physiology Score, *APACHE II* Acute Physiology and Chronic Health Evaluation, *V-POSSUM* Vascular Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity, *POSPOM* Preoperative Score to Predict Postoperative Mortality

* Mann–Whitney test

Table 4 Results of the multivariate analysis of mortality predictors

Variables	OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Age	**1.04 (1.01–1.07)**	**0.018**	**1.04 (1.01–1.08)**	**0.013**
Current smoker	**2.26 (1.19–4.30)**	**0.013**	**2.46 (1.16–5.21)**	**0.019**
Peripheral arterial disease	1.86 (1.00–3.46)	0.049	1.08 (0.48–2.44)	0.857
Congestive heart failure	3.58 (1.92–6.65)	< 0.001	1.87 (0.85–4.12)	0.122
Chronic kidney disease[a]	3.71 (1.79–7.69)	0.001	1.89 (0.70–5.11)	0.209
Emergent surgery	3.97 (1.91–8.25)	< 0.001	1.63 (0.62–4.30)	0.326
High-risk surgery	**6.94 (2.70–17.81)**	**< 0.001**	**2.92 (1.05–8.08)**	**0.040**
Mechanical ventilation	2.89 (1.55–5.40)	0.001	1.02 (0.44–2.37)	0.962
Systolic blood pressure	0.98 (0.97–0.99)	< 0.001	0.99 (0.98–1.00)	0.127
Heart rate	1.03 (1.02 -1.05)	< 0.001	1.04 (0.99–1.03)	0.149
Respiratory rate	1.16 (1.04–1.31)	0.010	1.04 (0.89–1.21)	0.614
Hematocrit	**0.84 (0.79–0.90)**	**< 0.001**	**0.86 (0.80–0.93)**	**< 0.001**
Serum urea	**1.02 (1.01–1.03)**	**< 0.001**	**1.01 (1.01–1.02)**	**0.001**
Serum creatinine	1.60 (1.28–2.00)	< 0.001	0.89 (0.60–1.33)	0.570
Serum sodium	**1.22 (1.15 -1.30)**	**< 0.001**	**1.17 (1.10–1.26)**	**< 0.001**
Leukocytes	**1.06 (1.02–1.10)**	**0.006**	**1.05 (1.01–1.10)**	**0.009**

The independent predictors are highlighted in bold

OR odds ratio, *CI* confidence interval

[a]Glomerular filtration rate < 60 ml/min

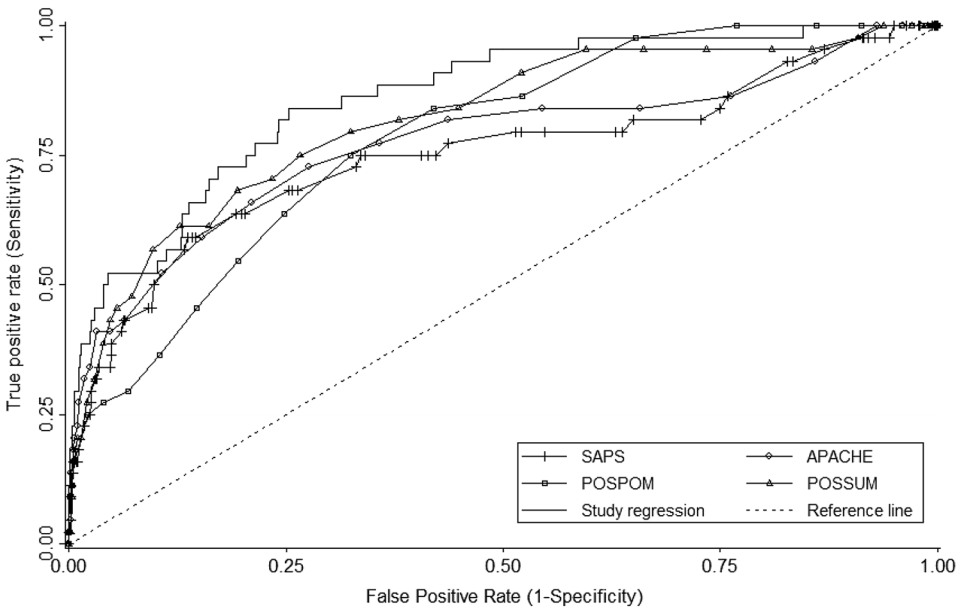

Fig. 1 Area under the receiver operating characteristic curve of the risk scores. *SAPS* Simplified Acute Physiology Score, *APACHE* Acute Physiology and Chronic Health Evaluation, *POSPOM* Preoperative Score to Predict Postoperative Mortality, *POSSUM* Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity

SAPS - Simplified Acute Physiology Score. APACHE - Acute Physiology and Chronic Health Evaluation. POSPOM - Preoperative Score to Predict Postoperative Mortality. POSSUM - Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity.

1–5% for intermediate-risk surgery and > 5% for high-risk surgery [24]. In our sample, we found similar mortality rates: 1.3% after intermediate-risk surgery and 8.4% after high-risk surgery. In our model, high-risk surgery was considered an independent risk factor increasing the risk of HM by almost threefold. Our results are consistent with previous studies showing that the mortality during ICU admission depends on the type of admission [8–10, 26, 27]. Patients undergoing emergent surgery may be more severely ill, with more uncontrolled comorbidities and a less functional reserve than in healthy patients. Furthermore, the surgeries can be more complex and intraoperative care may be suboptimal in these patients [10, 28].

In critical care, serum sodium levels have been associated with mortality [29–33]. Hypernatremia is a common complication, especially if patients are unconscious, intubated or sedated, and may indicate a hyperosmolar state and transiently intracellular dehydration [34]. In addition, age has also been associated with postoperative mortality, and the predictive ability of some scores varies according to age intervals [5, 8, 35, 36]. Both age and the serum sodium level remained independent predictors in our multivariate logistic regression analysis, which may explain why so many ICU or surgical risk scores include these parameters.

Patients who developed cardiovascular or renal complications had a higher mortality than those without such events. This has been studied in the past, and cardiovascular complications were implicated in 42% of deaths [10, 26, 37, 38]. An elevated serum urea level may reflect acute kidney injury, a known cause of increased mortality [39–42]. The LOS is also influenced by these complications along with severe illness, which may explain the differences observed [9, 37, 38, 43]. An active smoking status increases the risk of complications and mortality after surgery [44]. This may explain why the serum urea level and smoking status were considered independent predictors for mortality.

The hematocrit after surgery was an independent protective factor. Numerous studies have shown a relationship between the hematocrit or hemoglobin levels and the outcome, especially in VS patients with coronary heart disease [45–49]. Velescu et al. proved that patients with a preoperative hemoglobin level < 10 g/dl had an increased mortality rate with an adjusted OR of 3.9 [45]. Both anemia and perioperative red blood cell transfusion independently increase the risk of MACE and mortality, but unfortunately, we only had the hematocrit available for our analysis. This parameter may be considered a proxy for hemoglobin levels.

The preoperative patient evaluation using risk scores is much more objective than traditional observation-only assessment. The POSSUM score consists of 12 physiologic and 6 intraoperative variables. Even though authors advocate having scores for different surgeries (vascular, colorectal, esophagogastric), the models do not substantially differ between these procedures. Despite only using 12 physiologic variables, POSSUM was the best score for predicting HM in patients admitted to the SICU after VS in the present study. The mortality prediction with POSSUM ($n = 44$) was very close to what we observed ($n = 43$), resulting in an observed/expected ratio of 0.98. The POSPOM score was created to predict mortality after many types of surgery, so it is

unsurprising that it performed slightly worse than POSSUM. However, it has the advantage of using only preoperative variables, and the surgical specialty can be differentiated to some degree by adding more points according to the surgical risk. We, therefore, believe that it is also a good option for use in this situation. The SAPS and APACHE were specifically designed to predict mortality after ICU admission, and several modified versions of these scores have been developed over time. However, in the present cohort of patients submitted to VS, SAPS and APACHE performed worse than POSSUM or POSPOM and should be replaced by these surgical risk scores in ICU admission after surgery.

Several limitations associated with the present study warrant mention. We did not have access to data on all the intraoperative variables necessary to calculate the total POSSUM. Some scores consider the 30-day mortality, but we were only able to study the HM. In addition, we included patients encountered over a long period of time, and surgical techniques may have improved over time.

Conclusion

In conclusion, the HM in patients admitted to the SICU after open VS was 5.1%. The observed mortality was within the predicted range (1–5% after intermediate-risk and > 5% after high-risk surgery). The mortality group had significantly higher scores in SAPS, APACHE, POSSUM and POSPOM than the survival group. A longer LOS and cardiovascular and renal complications were associated with a higher HM. We identified the following independent risk factors for mortality: age, smoking status, surgery risk, serum sodium level, urea and leukocyte count at admission to the SICU. The surgical risk scores POSSUM and POSPOM predicted HM better than the ICU scores SAPS and APACHE in patients admitted to the SICU after VS.

Author contribution All authors were involved in data collection. PR was responsible for the data analysis and manuscript writing. FA coordinated the project and revised the manuscript. All authors approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest All authors have nothing to declare.

References

1. Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. Lancet. 2008;372(9633):139–44.
2. Gupta PK, Gupta H, Sundaram A, Kaushik M, Fang X, Miller WJ, et al. Development and validation of a risk calculator for prediction of cardiac risk after surgery. Circulation. 2011;124(4):381–7.
3. Ohlsson H, Winso O. Assessment of the surgical Apgar Score in a Swedish setting. Acta Anaesthesiol Scand. 2011;55(5):524–9.
4. Pearse RM, Moreno RP, Bauer P, Pelosi P, Metnitz P, Spies C, et al. Mortality after surgery in Europe: a 7 day cohort study. Lancet. 2012;380(9847):1059–65.
5. Monk TG, Saini V, Weldon BC, Sigl JC. Anesthetic management and one-year mortality after noncardiac surgery. Anesth Analg. 2005;100(1):4–10.
6. Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ, et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Ann Surg. 2005;242(3):326–41.
7. Ghaferi AA, Birkmeyer JD, Dimick JB. Variation in hospital mortality associated with inpatient surgery. N Engl J Med. 2009;361(14):1368–75.
8. Pearse RM, Harrison DA, James P, Watson D, Hinds C, Rhodes A, et al. Identification and characterisation of the high-risk surgical population in the United Kingdom. Crit Care. 2006;10(3):R81.
9. Abelha FJ, Castro MA, Landeiro NM, Neves AM, Santos CC. Mortality and length of stay in a surgical intensive care unit. Rev Br Anestesiol. 2006;56(1):34–45.
10. Leung JM, Dzankic S. Relative importance of preoperative health status versus intraoperative factors in predicting postoperative adverse outcomes in geriatric surgical patients. J Am Geriatr Soc. 2001;49(8):1080–5.
11. Hall BL, Hamilton BH, Richards K, Bilimoria KY, Cohen ME, Ko CY. Does surgical quality improve in the American College of Surgeons National Surgical Quality Improvement Program: an evaluation of all participating hospitals. Ann Surg. 2009;250(3):363–76.
12. Weissman C. The enhanced postoperative care system. J Clin Anesth. 2005;17(4):314–22.
13. Simpson JC, Moonesinghe SR. Introduction to the postanaesthetic care unit. Perioperat Med. 2013;2(1):5.
14. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10):818–29.
15. Vincent JL, Moreno R. Clinical review: scoring systems in the critically ill. Crit Care. 2010;14(2):207.
16. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. J Am Med Assoc. 1993;270(24):2957–63.
17. Halpern NA, Pastores SM, Greenstein RJ. Critical care medicine in the United States 1985-2000: an analysis of bed numbers, use, and costs. Crit Care Med. 2004;32(6):1254–9.
18. Mosquera D, Chiang N, Gibberd R. Evaluation of surgical performance using V-POSSUM risk-adjusted mortality rates. ANZ J Surg. 2008;78(7):535–9.
19. Midwinter MJ, Tytherleigh M, Ashley S. Mortality and morbidity risk in Vascular Surgery using POSSUM and Portsmouth predictor equation. Br J Surg. 1999;86:471–4.
20. Le Manach Y, Collins G, Rodseth R, Le Bihan-Benjamin C, Biccard B, Riou B, et al. Preoperative Score to Predict Postoperative Mortality (POSPOM): derivation and Validation. Anesthesiology. 2016;124(3):570–9.
21. Liu Y, Cohen ME, Ko CY, Bilimoria KY, Hall BL. Considerations in releasing equations for the american college of surgeons NSQIP surgical risk calculator in: reply to Wanderer and Ehrenfeld. J Am Coll Surg. 2016;223(4):674–5.
22. Bilimoria KY, Liu Y, Paruch JL, Zhou L, Kmiecik TE, Ko CY, et al. Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons. J Am Coll Surg. 2013;217(5):833–42.

23. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370:1453–7.
24. Kristensen SD, Knuuti J, Saraste A, Anker S, Botker HE, De Hert S, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: the Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). Eur J Anaesthesiol. 2014;31(10):517–73.
25. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11(2):R31.
26. Devereaux PJ, Chan MT, Alonso-Coello P, Walsh M, Berwanger O, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. J Am Med Assoc. 2012;307(21):2295–304.
27. Rhodes A, Moreno RP, Metnitz B, Hochrieser H, Bauer P, Metnitz P. Epidemiology and outcome following post-surgical admission to critical care. Intensive Care Med. 2011;37(9):1466–72.
28. Weissman C, Klein N. The importance of differentiating between elective and emergency postoperative critical care patients. J Crit Care. 2008;23(3):308–16.
29. Darmon M, Diconne E, Souweine B, Ruckly S, Adrie C, Azoulay E, et al. Prognostic consequences of borderline dysnatremia: pay attention to minimal serum sodium change. Crit Care. 2013;17(1):R12.
30. Funk GC, Lindner G, Druml W, Metnitz B, Schwarz C, Bauer P, et al. Incidence and prognosis of dysnatremias present on ICU admission. Intensive Care Med. 2010;36(2):304–11.
31. Darmon M, Timsit JF, Francais A, Nguile-Makao M, Adrie C, Cohen Y, et al. Association between hypernatraemia acquired in the ICU and mortality: a cohort study. Nephrol Dial Transplant. 2010;25(8):2510–5.
32. Waite MD, Fuhrman SA, Badawi O, Zuckerman IH, Franey CS. Intensive care unit-acquired hypernatremia is an independent predictor of increased mortality and length of stay. J Crit Care. 2013;28(4):405–12.
33. Stelfox HT, Ahmed SB, Khandwala F, Zygun D, Shahpori R, Laupland K. The epidemiology of intensive care unit-acquired hyponatraemia and hypernatraemia in medical–surgical intensive care units. Crit Care. 2008;12(6):R162.
34. Lindner G, Funk GC. Hypernatremia in critically ill patients. J Crit Care. 2013;28(2):216.
35. Naughton C, Feneck RO. The impact of age on 6-month survival in patients with cardiovascular risk factors undergoing elective non-cardiac surgery. Int J Clin Pract. 2007;61(5):768–76.
36. Skonetzki S, Lüders F, Engelbertz C, Malyar NM, Freisinger E, Meyborg M, et al. Aging and outcome in patients with peripheral artery disease and critical limb ischemia. J Post-Acute Long-Term Care Med. 2016;17(10):927–32.
37. Maia PC, Abelha FJ. Predictors of major postoperative cardiac complications in a surgical ICU. Portug J Cardiol. 2008;27(3):321–8.
38. Abelha FJ, Botelho M, Fernandes V, Barros H. Quality of life and mortality assessment in patients with major cardiac events in the postoperative period. Rev Br Anestesiol. 2010;60(3):268–84.
39. Flores E, Lewinger JP, Rowe VL, Woo K, Weaver FA, Shavelle D, et al. Increased risk of mortality after lower extremity bypass in individuals with acute kidney injury in the vascular quality initiative. J Vasc Surg. 2017;65(4):1055–61.
40. Huber M, Ozrazgat-Baslanti T, Thottakkara P, Efron PA, Feezor R, Hobson C, et al. Mortality and cost of acute and chronic kidney disease after vascular surgery. Ann Vasc Surg. 2016;30:72–81.
41. Arora P, Davari-Farid S, Pourafkari L, Gupta A, Dosluoglu HH, Nader ND, et al. The effect of acute kidney injury after revascularization on the development of chronic kidney disease and mortality in patients with chronic limb ischemia. J Vasc Surg. 2015;61(3):720–7.
42. O'Hare AM, Sidawy AN, Feinglass J, Merine KM, Daley J, Khuri S, et al. Influence of renal insufficiency on limb loss and mortality after initial lower extremity surgical revascularization. J Vasc Surg. 2004;39(4):709–16.
43. Lobo SM, Rezende E, Knibel MF, Silva NB, Paramo JA, Nacul FE, et al. Early determinants of death due to multiple organ failure after noncardiac surgery in high-risk patients. Anesth Analg. 2011;112(4):877–83.
44. Chen SL, Whealon MD, Kabutey NK, Kuo IJ, Sgroi MD, Fujitani RM. Outcomes of open and endovascular lower extremity revascularization in active smokers with advanced peripheral arterial disease. J Vasc Surg. 2017;65(6):1680–9.
45. Velescu A, Clará A, Cladellas M, Peñafiel J, Mateos E, Ibañez S, et al. Anemia increases mortality after open or endovascular treatment in patients with critical limb ischemia: a retrospective analysis. Eur J Vasc Endovasc Surg. 2016;51(4):543–9.
46. Ad N, Holmes SD, Massimiano PS, Spiegelstein D, Shuman DJ, Pritchard G, et al. Operative risk and preoperative hematocrit in bypass graft surgery: role of gender and blood transfusion. Cardiovasc Revasc Med. 2015;16(7):397–400.
47. Gupta PK, Sundaram A, MacTaggart JN, Johanning JM, Gupta H, Fang X, et al. Preoperative anemia is an independent predictor of postoperative mortality and adverse cardiac events in elderly patients undergoing elective vascular operations. Ann Surg. 2013;258(6):1096–102.
48. Valentijn TM, Hoeks SE, Bakker EJ, van de Luijtgaarden KM, Verhagen HJ, Stolker RJ, et al. The impact of perioperative red blood cell transfusions on postoperative outcomes in vascular surgery patients. Ann Vasc Surg. 2015;29(3):511–9.
49. O'Keeffe SD, Davenport DL, Minion DJ, Sorial EE, Endean ED, Xenos ES. Blood transfusion is associated with increased morbidity and mortality after lower extremity revascularization. J Vasc Surg. 2010;51(3):616–21.

Paper C

Article

Major Cardiac Events in Patients Admitted to Intensive Care After Vascular Noncardiac Surgery: A Retrospective Cohort

Seminars in Cardiothoracic and Vascular Anesthesia
2019, Vol. 23(3) 293–299

DOI: 10.1177/1089253218825442
journals.sagepub.com/home/scv
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Abstract

Introduction. Patients proposed to vascular noncardiac surgery (VS) have several comorbidities associated with major adverse cardiac events (MACE). We evaluated incidence, predictors, and outcomes, and compared different scores to predict MACE after VS. *Methods*. We included all patients admitted from 2006 to 2013. Perioperative MACE included cardiac arrhythmias, myocardial infarction (MI), cardiogenic pulmonary edema (CPE), acute heart failure (AHF), and cardiac arrest (CA). Lee Revised Cardiac Risk Index (RCRI), Vascular Quality Initiative (VQI-CRI), Vascular Study Group of New England (VSG-CRI), and South African Vascular Surgical (SAVS-CRI) Cardiac Risk Indexes were calculated and analyzed. We performed multivariate logistic regression to assess independent predictors with calculation of odds ratio (OR) and 95% confidence interval (CI). To reduce overfitting, we used leave-one-out cross-validation approach. The Predictive ability of scores was tested using area under receiver operating characteristic curve (AUROC). *Results*. A total of 928 patients were included. We observed 81 MACE (28 MI, 22 arrhythmias, 10 CPE, 9 AHF, 12 CA) in 60 patients (6.5%): 3.3% in intermediate-risk surgery and 9.8% in high-risk surgery. Previous history of coronary artery disease (OR = 3.2, CI = 1.8-5.7), atrial fibrillation (OR = 5.1, CI = 2.4-11.0), insulin-treated diabetes mellitus (OR = 3.26, CI = 1.51-7.06), mechanical ventilation (OR = 2.75, CI = 1.41-4.63), and heart rate (OR = 1.02, CI = 1.01-1.03) at admission were considered independent risk factors in multivariate analysis. The AUROC of our model was 0.79, compared with RCRI (0.66), VSG-CRI (0.69), VQI-CRI (0.71), and SAVS-CRI (0.73). *Conclusions*. Observed MACE were within predicted range (1% to 5% after intermediate-risk surgery and >5% after high-risk surgery). SAVS-CRI and VQI-CRI had slightly better predictive capacity than VSG-CRI or RCRI.

Keywords

cardiac arrhythmia, myocardial infarction, pulmonary edema, heart failure, cardiac arrest, intensive care unit, vascular surgery

Introduction

Perioperative major adverse cardiac events (MACE) are common and increase length of hospital stay and mortality.[1] Lee et al[2] defined MACE as myocardial infarction, pulmonary edema (confirmed by chest radiograph in a plausible clinical setting), ventricular fibrillation or primary cardiac arrest (CA), and complete heart block. Patients submitted to vascular noncardiac surgery (VS) have several cardiovascular risk factors that are associated with MACE.[3] The risk depends not only on patient or surgical factors but also on intra- or postoperative parameters.[1,3,4] Hemodynamic instability, blood loss, aortic cross clamping, reperfusion phenomena, and arterial embolism may increase the risk of complications after VS.[4]

Perioperative myocardial injury is often undetected because it does not exhibit typical symptoms of myocardial ischemia, such as chest pain, angina pectoris, or dyspnea.[5] Acute myocardial infarction (MI) after major VS may

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Table 1. Comparison of the Different Cardiac Risk Scores[a].

RCRI	VQI-CRI[b]	VSG-CRIs	SAVS-CRI
High-risk surgery (1)[c]	Age	Age (2-4)	Age >65 years (2)
Ischemic heart disease (1)	Ischemic heart disease	Ischemic heart disease (2)	Ischemic heart disease (2)
Congestive heart failure (1)	Congestive heart failure	Congestive heart failure (2)	Suprainguinal surgery (7)
Cerebrovascular disease (1)	Chronic obstructive pulmonary disease	Chronic obstructive pulmonary disease (2)	Intermediate-risk surgery (3)
Insulin-treated diabetes mellitus (1)	Diabetes mellitus	Insulin-treated diabetes mellitus (1)	Diabetes mellitus (2)
Chronic kidney disease (creatinine >2.0 mg/dL) (1)	Chronic kidney disease (creatinine >1.8 mg/dL)	Chronic kidney disease (creatinine >1.8 mg/dL) (2)	β-blocker therapy (4)
	Critical limb ischemia	Current smoker (1)	CABG or PCI (-3)
	Arterial hypertension	β-blocker therapy (1)	
	Abnormal cardiac stress test	CABG or PCI (−1)	
	Body mass index		

Abbreviations: RCRI, Revised Cardiac Risk Index; VQI, Vascular Quality Initiative; CRI, Cardiac Risk Index; VSG, Vascular Study Group of New England; SAVS, South African Vascular Surgery; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.
[a]Points in parenthesis.
[b]Included variables and their relative weight is dependent on type of surgery.
[c]Suprainguinal vascular, intrathoracic, or intraperitoneal procedures.

range from 0.3% to 36%.[6] This is why some authors recommend troponin screening after surgery.[7] An accurate preoperative risk assessment is essential to guide patient management, allowing appropriate medical optimization, establish cardiac interventions, and early detect possible complications.[8]

Lee Revised Cardiac Risk Index (RCRI)[2] includes 6 independent predictors: high-risk type of surgery (suprainguinal vascular, intrathoracic, or intraperitoneal procedures); history of ischemic heart disease; history of congestive heart failure; history of cerebrovascular disease; preoperative treatment with insulin; and renal insufficiency (preoperative serum creatinine >2.0 mg/dL).[2] Although extensively used, RCRI may not be the best score to predict MACE after VS.[9]

More recently, Vascular Quality Initiative (VQI-CRI),[10] Vascular Study Group of New England (VSG-CRI),[11] and South African Vascular Surgical (SAVS-CRI)[12] Cardiac Risk Indexes were derived to predict MACE after VS. The VQI-CRI has 5 variants depending on the surgery performed: carotid endarterectomy, endovascular aneurysm repair, open abdominal aortic aneurysm repair, suprainguinal bypass, and infrainguinal bypass. Age, type of surgery, history of coronary artery disease, diabetes, and creatinine concentration >1.8 mg/dL are included in all scores (Table 1). Only VQI-CRI uses critical limb ischemia, arterial hypertension, stress test status, and body mass index as predictors, whereas VSG-CRI and SAVS-CRI use chronic β-blockers as a risk factor and previous coronary surgery/percutaneous intervention as protective.

Our primary aim was to evaluate the incidence of MACE and its impact on the outcome of patients admitted to intensive care unit (ICU) after VS. Additionally, we wanted to identify and stratify the risk factors for MACE and compare the existing risk scores to predict MACE.

Methods

Study Design, Setting, and Participants

Retrospective cohort including all patients admitted to the surgical ICU after VS from January 2006 to July 2013 in a large academic hospital. We planned the analysis before looking at the data; exposures and outcomes were previously defined. The institutional ethics committee approved the protocol. This report complies with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational cohort studies.[13]

Data Collection

We prospectively collected the following variables at ICU admission: age, gender, medical history, type of admission (elective or emergent), type of surgery, and ventilation. Surgeries were divided into intermediate-risk or high-risk surgery according to the joint guidelines of the European Society of Cardiology (ESC) and European Society of Anesthesiology (ESA).[14] During ICU stay, prospective records included vital signs, laboratory results, and MACE such as cardiac arrhythmias, MI, cardiogenic pulmonary edema (CPE), acute heart failure (AHF), and CA. Acute MI was defined following the ESC/American College of Cardiology criteria.[15] We also analyzed hospital or ICU mortality and length of stay (LOS). The ICU records at

Table 2. Univariate Analysis of Major Adverse Cardiac Events (MACE).

Variables	No MACE Group (n = 868)	MACE Group (n = 60)	*P*
Age in years, median (IQR)	69 (61-76)	70 (60-77)	.458[a]
Male gender, n (%)	697 (80.3)	47 (78.3)	.712[b]
Prior medical history, n (%):			
Arterial hypertension	438 (50.5)	31 (51.7)	.857[b]
Diabetes mellitus	200 (23.0)	19 (31.7)	.128[b]
Current smoker	182 (21.0)	13 (21.7)	.898[b]
Peripheral arterial disease	250 (28.8)	22 (36.7)	.196[b]
Coronary artery disease	278 (32.0)	35 (58.3)	**<.001**[b]
Congestive heart failure	206 (23.7)	30 (50.0)	**<.001**[b]
Atrial fibrillation	46 (5.3)	12 (20.0)	**<.001**[b]
Cerebrovascular disease	350 (40.3)	19 (31.7)	.185[b]
Chronic kidney disease	82 (9.4)	10 (16.7)	.070[b]
Emergent surgery, n (%)	71 (8.2)	10 (16.7)	**.025**[b]
High-risk surgery, n (%)	416 (48.3)	45 (75.0)	**<.001**[b]
Endovascular surgery, n (%)	91 (10.5)	7 (11.7)	.773[b]
At admission			
Mechanical ventilation, n (%)	174 (20.0)	29 (48.3)	**<.001**[b]
Vasopressors, n (%)	6 (0.7)	6 (10.0)	**<.001**[b]
Body temperature, median (IQR)	35.8 (34.9-36.1)	35.8 (34.2-36.0)	.248[a]
Systolic pressure, median (IQR)	132 (109-158)	119 (97-148)	**.007**[a]
Mean arterial pressure, median (IQR)	89 (73-101)	82 (66-97)	**.020**[a]
Heart rate, median (IQR)	78 (65-89)	88 (72-105)	**<.001**[a]
Hematocrit, median (IQR)	33.0 (29.5-36.0)	30.6 (26.0-36.9)	**.021**[a]
Serum urea, median (IQR)	33 (25-44)	40 (30-60)	**.009**[a]
Serum creatinine, median (IQR)	0.9 (0.7-1.2)	1.1 (0.8-1.8)	**.001**[a]
Serum potassium, median (IQR)	3.8 (3.5-4.1)	4.0 (3.5-4.3)	.155[a]
Serum sodium, median (IQR)	139 (137-141)	139 (137-144)	.073[a]
Leucocytes count, median (IQR)	10.2 (7.6-12.7)	12.4 (9.9-14.1)	**.002**[a]
Length of stay (hours), median (IQR)	21 (16-43)	45 (21-90)	**<.001**[a]
Hospital mortality, n (%)	28 (3.2)	16 (26.7)	**<.001**[b]

Abbreviation: IQR, interquartile range (P25-P75).
[a]Mann-Whitney test.
[b]Chi-square test.

admission include the RCRI, whereas VSG-CRI, VQI-CRI, and SAVS-CRI were calculated in retrospective. We computed VQI-CRI according to the surgery performed.

Statistical Analysis

We used descriptive statistics to summarize data. We performed Kolmogorov-Smirnov test and histogram analysis to assess normality of data, and we selected parametric (independent samples *t* test) or nonparametric tests (Mann-Whitney *U*) accordingly. To compare proportions between groups in univariate analysis, we used the χ^2 test. We determined independent predictors of MACE using multivariate logistic regression with forward conditional method, calculating odds ratio (OR) and its 95% confidence interval (CI). We created a model using the adjusted OR of the independent variables as scoring points and analyzed the area under receiver operating characteristic (AUROC) of the different risk indexes to measure their predictive discrimination. We used the Hosmer-Lemeshow test to determine the goodness of fit of our model (calibration), $P > .05$ for no significant difference between predictive model and observed data. To reduce the potential of overfitting, we selected the leave-one-out cross-validation approach and the bootstrapping method. We performed Bonferroni correction for multiple comparisons. We used Stata 14 and SPSS 23 to analyze the data.

Results

During the study period, 928 patients were admitted to ICU after VS, and most of them were male. We included high-risk (open aortic surgery, lower limb revascularization or thromboembolectomy or amputation) and intermediate-risk surgeries (carotid endarterectomy, peripheral angioplasty, or endovascular aortic aneurysm repair). We

Table 3. Cardiac Risk Indexes by Major Adverse Cardiac Events (MACE).

Risk Scores	No MACE Group (n = 884)	MACE Group (n = 44)	*P*
RCRI, median (IQR)	1 (1-2)	2 (1-3)	**<.001**[a]
VQI-CRI, median (IQR)	7.3 (5.9-8.9)	9.3 (7.4-11.3)	**<.001**[a]
VSG-CRI, median (IQR)	4 (2-6)	6 (4-9)	**<.001**[a]
SAVS-CRI, median (IQR)	7 (5-9)	11 (8-13)	**<.001**[a]

Abbreviations: RCRI, Revised Cardiac Risk Index; IQR, interquartile range (P25-P75); VQI, Vascular Quality Initiative; CRI, Cardiac Risk Index; VSG, Vascular Study Group of New England; SAVS, South African Vascular Surgery.
[a]Mann-Whitney test.

Table 4. Multivariate Analysis of Major Adverse Cardiac Events' Predictors.

Variables	OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*	Model Points
Coronary artery disease	**2.97 (1.74-5.06)**	**<.001**	**3.18 (1.78-5.70)**	**<.001**	**3**
Congestive heart failure	3.21 (1.89-5.46)	<.001	—	—	
Atrial fibrillation	**4.47 (2.22-8.99)**	**<.001**	**5.13 (2.39-11.00)**	**<.001**	**5**
Diabetes mellitus[a]	**3.75 (1.84-7.67)**	**<.001**	**3.26 (1.51-7.06)**	**.003**	**3**
Emergent surgery	2.25 (1.09-4.62)	.028	—	—	
High-risk surgery	3.22 (1.77-5.86)	<.001	—	—	
Mechanical ventilation	**3.73 (2.19-6.36)**	**<.001**	**2.75 (1.52-4.99)**	**.001**	**3**
Systolic blood pressure	0.98 (0.97-0.99)	.012	—	—	
Heart rate continuous	1.03 (1.01-1.04)	<.001	1.02 (1.01-1.03)	.002	
Heart rate ordinal[b]	**1.70 (1.27-2.28)**	**<.001**	**1.51 (1.11-2.06)**	**.006**	**1.5 increase per group**[b]
Hematocrit	0.92 (0.88-0.97)	.002	—	—	
Serum urea	1.01 (1.01-1.02)	.001	—	—	
Serum creatinine	1.35 (1.11-1.63)	.002	—	—	

Abbreviations: OR, odds ratio; CI, confidence interval.
[a]Insulin-treated diabetes mellitus.
[b]Heart rate points: 0 if <60; 1.5 if 60 to 80; 3 if 80 to 100; 4.5 if >100 beats per minute.

observed 81 MACE (28 MI, 22 arrhythmias, 10 CPE, 9 AHF, and 12 CA) in 60 patients, representing an incidence of 6.5%: 3.3% in intermediate-risk surgery and 9.8% in high-risk surgery. Incidence of MI was 3.0% (28 out of 928 patients). Table 2 presents distribution of variables by MACE. Regarding type of admission, MACE incidence after elective surgery was 5.9% versus 12.3% after emergent surgery. Endovascular approach represented 10.8% of surgeries, and MACE incidence was no different from open surgery. Type of admission was not different in patients submitted to endovascular procedures; however, the endovascular group was older: 73 versus 67 years, $P < .001$. Type of ventilation (controlled vs spontaneous) but not surgery type increased ICU mortality and LOS. Carotid surgery (95% were submitted to cervical block regional anesthesia) had less MACE than lower limb or aortic surgery, 3.6% versus 8.1% versus 8.5%, respectively ($P = .005$).

Table 3 displays the scores of the different cardiac risk indexes. All were significantly higher ($P < .001$) in the MACE group. Table 4 shows the multiple logistic regression used to assess the effect of variables on MACE at preadmission and at admission (the first OR column represents the univariate analysis OR while the adjusted OR column represents the forward selection). The surgery type was included in the multivariate analysis to control and adjust for confounding variables. Previous history of coronary artery disease, atrial fibrillation, insulin-treated diabetes mellitus, mechanical ventilation, and heart rate at admission were considered independent predictors. They increase the risk of MACE regardless of surgery type. The scoring system was based on the OR values for these factors, which were rounded to the nearest whole number. To include heart rate in our model, we used a categorical variable: <60; 60 to 80; 80 to 100; >100 beats per minute. The OR was 1.5 for every unit increase in that ordinal variable resulting in 0 to 4.5 model points (Table 4). Predictive ability remained the same after this transformation. Although hospital LOS and mortality differ between intermediate-risk and high-risk surgery, MACE remained an independent risk factor for mortality after adjusting for surgery type: OR 9.9 (5.0-19.9).

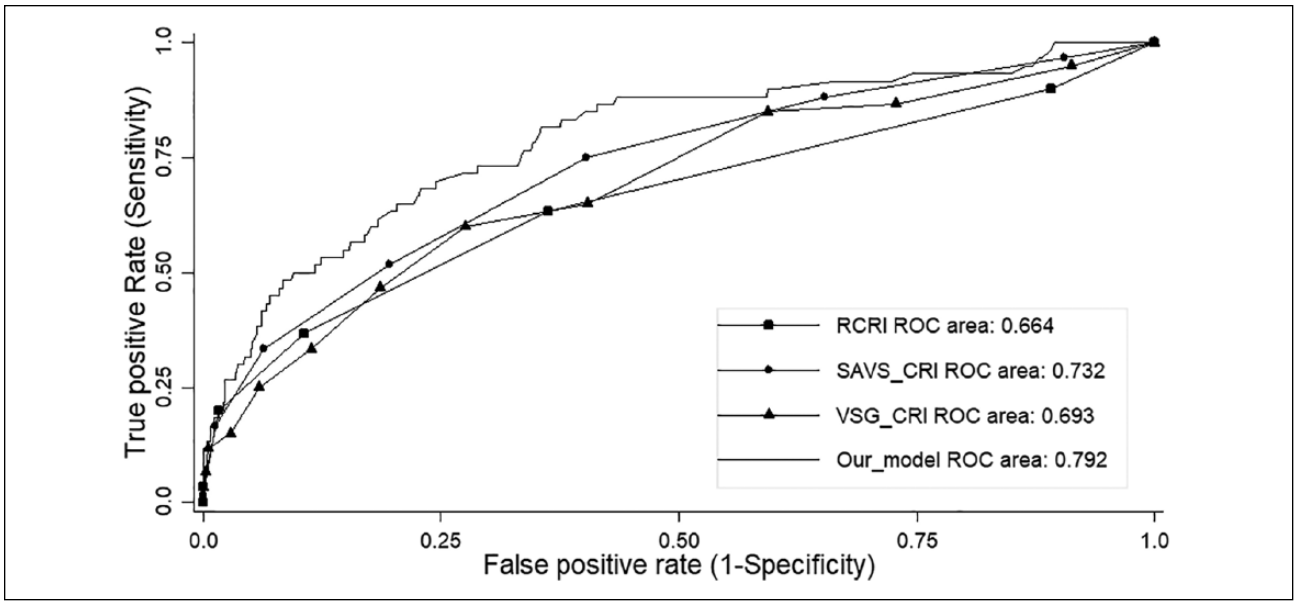

Figure 1. Receiver Operating Characteristics (ROC) Curve of the different Cardiac Risk Indexes.

Figure 1 graphically displays the AUROC of the different scores. Our model had an AUROC of 0.79 with a Hosmer-Lemeshow test for the goodness of fit of 0.232 (good calibration). After leave-one-out cross-validation and bootstrapping, we obtained a similar AUROC of 0.77. The AUROC of RCRI (0.66) and VSG-CRI (0.69) were slightly worse than VQI-CRI (0.71) and SAVS-CRI (0.73). When comparing our model with the other scores, the *P* values were $<.001$ for RCRI, .002 for VSG-CRI, .0140 for VQI-CRI, and .0218 for SAV-CRI. After Bonferroni correction, only the *P* values for VSG-CRI and RCRI remained significant ($P < .0125$).

Discussion

Exact mechanisms of perioperative myocardial ischemia remain yet to be fully understood with multiple possible contributors. Postoperative period is potentially critical since sedation/analgesia may blunt any symptoms.[5,16] We believe that it is important to have an established protocol to systematically collect information to early detect MACE or MI. Definition of MACE or MI is different between studies and may explain some incidence variability (from 0.3% to 36%).[6] Included surgeries and outcome measurements may also contribute to the disparity. Acute MI and MACE were prospectively collected in a cohort of 928 patients submitted to VS. Incidence of MACE was within the predicted range of ESC/ESA guidelines[14] (1% to 5% after intermediate-risk surgery and >5% after high-risk surgery).

Medical history of atrial fibrillation, ischemic heart disease, or insulin-treated diabetes mellitus have been previously identified as risk factors for MACE.[2] The last 2 are included in RCRI and VSG, whereas VQI and SAVS include all diabetic patients. Bakker et al[3] evaluated MACE in 1462 patients submitted to VS and reported that type 2 diabetes mellitus, independent of insulin use, is associated with an increased risk of cardiac complications after vascular surgery. Vanniyasingam et al[17] also reported diabetes, together with brain natriuretic peptide, as risk factors for MACE after VS.

Both intra- and postoperative factors may contribute to MACE. van Lier et al[1] described tachycardia, anemia, hypoxemia, and hypotension as contributors to myocardial injury because of a supply and demand mismatch. We found mechanical ventilation and heart rate at admission to ICU as independent risk factors for MACE after VS. Scali et al[18] reported less mortality when heart rate was less than 75 beats per minute, but the effect disappeared after controlling for β-blocker therapy. Unfortunately, it was impossible to determine β-blocker therapy in our sample.

A systematic review of 24 studies (792 740 patients) using the RCRI to predict MACE reported an AUROC of 0.75 for noncardiac surgery but less accurate (0.64) after VS.[9] RCRI discriminates moderately well between patients at high versus low risk for MACE after noncardiac surgery; however, patients submitted to VS are at increased risk, especially because our sample includes intermediate-risk and high-risk surgery.[9] Biomarkers such as brain natriuretic peptide, C-reactive protein, or copeptin may be used to predict outcomes after VS and improve the risk stratification capacity of the RCRI.[19-22] Another way of improving the RCRI is using age and history of arterial hipertension.[23] This was not true in our sample since age did not influence the risk of MACE. Despite the 5 variants of VQI depending

on the surgery performed, its AUROC was similar to VSG or SAVS. The performance of the scores was better than previously reported in earlier studies.[24,25] All use serum creatinine to define chronic kidney disease, but they may be updated to use creatinine clearance in the near future.[26]

Prediction is also influenced by the correct measurement of the outcomes. Some authors advocate troponin measurements systematically during the first 3 to 5 days after surgery.[27-29] High-sensitive troponin may be more sensitive but not as specific. These measurements are important regardless of symptoms because only 6% of patients have typical chest pain.[5] In our study, acute MI and MACE were prospectively and systematically collected during ICU stay, but during that period, we used regular instead of high-sensitivity troponin. The exact values of troponin may influence short-term and long-term mortality until 5 years after surgery.[30]

Some risk scores predict mortality/morbidity after VS but do not discriminate the site of complications. Others are specific for MACE but were developed including many types of noncardiac surgery and not specifically VS. Gupta et al reported that perioperative risk for myocardial infarction or cardiac arrest[31] allows differentiating the type of surgery, but we did not have the functional status data to calculate it. The American College of Surgeons developed a surgical risk calculator, but authors did not make the equation available for clinical research to protect intellectual property and because they thought that external validation was not necessary.

Although all scores include age as a risk factor, we did not find it in our study. This may be because older patients were submitted to less invasive endovascular procedures, also explaining why endovascular had the same MACE incidence as open surgery. Despite a better prediction using our model, its usefulness in stratifying preoperative risk may be limited since some variables refer to parameters at admission to ICU. The sample size led authors to use the leave-one-out cross-validation approach and the bootstrapping method instead of the division into derivation and validation cohort. This is a limitation considering our model, but it does not interfere with the comparison of the other scores. Another limitation is that we have vital signs at ICU admission but not during the intraoperative period. In addition, we used only intermediate-risk or high-risk surgical patients admitted to the surgical ICU and recorded MACE only during ICU stay.

Conclusions

Observed MACE were within the predicted range (1% to 5% after intermediate-risk surgery and >5% after high-risk surgery). Previous history of coronary artery disease, atrial fibrillation, insulin-treated diabetes mellitus, mechanical ventilation, and heart rate at admission were considered independent risk factors. The SAVS-CRI and VQI-CRI had slightly better predictive capacity than the VSG-CRI or the RCRI.

Author Contributions

All authors were involved in data collection. Pedro Videira Reis was responsible for data analysis and manuscript writing. Fernando Abelha coordinated the project and revised the manuscript. All authors approved the final version of the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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References

1. van Lier F, Wesdorp F, Liem VGB, et al. Association between postoperative mean arterial blood pressure and myocardial injury after noncardiac surgery. *Br J Anaesth*. 2018;120:77-83.
2. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation*. 1999;100:1043-1049.
3. Bakker EJ, Valentijn TM, van de Luijtgaarden KM, et al. Type 2 diabetes mellitus, independent of insulin use, is associated with an increased risk of cardiac complications after vascular surgery. *Anaesth Intensive Care*. 2013;41:584-590.
4. Biccard BM, Scott DJA, Chan MTV, et al. Myocardial injury after noncardiac surgery (MINS) in vascular surgical patients: a prospective observational cohort study. *Ann Surg*. 2018;268:357-363.
5. Puelacher C, Buse GL, Seeberger D, et al. Perioperative myocardial injury after noncardiac surgery: incidence, mortality, and characterization. *Circulation*. 2018;137:1221-1232.
6. Ollila A, Vikatmaa L, Virolainen J, et al. Perioperative myocardial infarction in non-cardiac surgery patients: a prospective observational study. *Scand J Surg*. 2017;106:180-186.
7. Liem VGB, Hoeks SE, Grüne F, et al. Prognostic value of postoperative high-sensitivity troponin T in patients with different stages of kidney disease undergoing noncardiac surgery. *Br J Anaesth*. 2018;120:84-93.
8. Liu JB, Liu Y, Cohen ME, Ko CY, Sweitzer BJ. Defining the intrinsic cardiac risks of operations to improve preoperative cardiac risk assessment. *Anesthesiology*. 2018;128:283-292.
9. Ford MK, Beattle WS, Wijeysundera DN. Systematic review: prediction of perioperative cardiac complications and mortality by the Revised Cardiac Risk Index. *Ann Intern Med*. 2010;152:26-35.

10. Bertges DJ, Neal D, Schanzer A, et al. The Vascular Quality Initiative Cardiac Risk Index for prediction of myocardial infarction after vascular surgery. *J Vasc Surg*. 2016;64:1411-1421.e4.
11. Bertges DJ, Goodney PP, Zhao Y, et al. The Vascular Study Group of New England Cardiac Risk Index (VSG-CRI) predicts cardiac complications more accurately than the Revised Cardiac Risk Index in vascular surgery patients. *J Vasc Surg*. 2010;52:674-683,683.e1-683.e3.
12. Moodley Y, Naidoo P, Biccard BM. The South African Vascular Surgical Cardiac Risk Index (SAVS-CRI): a prospective observational study. *S Afr Med J*. 2013;103:746-750.
13. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370:1453-1457.
14. Kristensen SD, Knuuti J, Saraste A, et al; Authors/Task Force Members. 2014 ESC/ESA guidelines on non-cardiac surgery: cardiovascular assessment and management: the Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). *Eur J Anaesthesiol*. 2014;31:517-573.
15. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined—a consensus document of the Joint European Society of Cardiology/American College of Cardiology committee for the redefinition of myocardial infarction. *J Am Coll Cardiol*. 2000;36:959-969.
16. Biccard BM. Detection and management of perioperative myocardial ischemia. *Curr Opin Anaesthesiol*. 2014;27:336-343.
17. Vanniyasingam T, Rodseth RN, Buse GAL, et al. Predicting the occurrence of major adverse cardiac events within 30 days of a vascular surgery: an empirical comparison of the minimum p value method and ROC curve approach using individual patient data meta-analysis. *Springerplus*. 2016;5:304.
18. Scali S, Bertges D, Neal D, et al. Heart rate variables in the Vascular Quality Initiative are not reliable predictors of adverse cardiac outcomes or mortality after major elective vascular surgery. *J Vasc Surg*. 2015;62:710-720.e9.
19. Schrimpf C, Gillmann HJ, Sahlmann B, et al. Renal function interferes with copeptin in prediction of major adverse cardiac events in patients undergoing vascular surgery. *PLoS One*. 2015;10:e0123093.
20. Jarai R, Mahla E, Perkmann T, et al. Usefulness of pre-operative copeptin concentrations to predict post-operative outcome after major vascular surgery. *Am J Cardiol*. 2011;108:1188-1195.
21. Patelis N, Kouvelos GN, Koutsoumpelis A, Moris D, Matsagkas MI, Arnaoutoglou E. An update on predictive biomarkers for major adverse cardiovascular events in patients undergoing vascular surgery. *J Clin Anesth*. 2016;33:105-116.
22. Singh TP, Morris DR, Smith S, Moxon JV, Golledge J. Systematic review and meta-analysis of the association between C-reactive protein and major cardiovascular events in patients with peripheral artery disease. *Eur J Vasc Endovasc Surg*. 2017;54:220-233.
23. Welten GM, Schouten O, van Domburg RT, et al. The influence of aging on the prognostic value of the revised cardiac risk index for postoperative cardiac complications in vascular surgery patients. *Eur J Vasc Endovasc Surg*. 2007;34:632-638.
24. Parmar CD, Torella F. Prediction of major adverse cardiac events in vascular surgery: are cardiac risk scores of any practical value? *Vasc Endovascular Surg*. 2010;44:14-19.
25. Smeili LA, Lotufo PA. Incidence and predictors of cardiovascular complications and death after vascular surgery. *Arq Bras Cardiol*. 2015;105:510-518.
26. Rochanov PS, Walsh M, Deveraux PJ, et al. External validation of the Revised Cardiac Risk Index and update of its renal variable to predict 30-day risk of major cardiac complications after non-cardiac surgery: rationale and plan for analyses of the VISION study. *BMJ Open*. 2017;7:e013510.
27. Gillmann HJ, Meinders A, Grohennig A, et al. Perioperative levels and changes of high-sensitivity troponin T are associated with cardiovascular events in vascular surgery patients. *Crit Care Med*. 2014;42:1498-1506.
28. Sessler DI, Devereaux PJ. Perioperative troponin screening. *Anesth Analg*. 2016;123:359-360.
29. Thomas KN, Cotter JD, Williams MJ, van Rij AM. Diagnosis, incidence, and clinical implications of perioperative myocardial injury in vascular surgery. *Vasc Endovasc Surg*. 2016;50:247-255.
30. Reed GW, Horr S, Young L, et al. Associations between cardiac troponin, mechanism of myocardial injury, and long-term mortality after noncardiac vascular surgery. *J Am Heart Assoc*. 2017;6:e005672.
31. Gupta PK, Gupta H, Sundaram A, et al. Development and validation of a risk calculator for prediction of cardiac risk after surgery. *Circulation*. 2011;124:381-387.

Paper D

International Journal of Surgery 73 (2020) 89–93

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.elsevier.com/locate/ijsu

Original Research

Incidence, predictors and validation of risk scores to predict postoperative mortality after noncardiac vascular surgery, a prospective cohort study

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ARTICLE INFO

Keywords:
Vascular surgery
Mortality
Surgical Apgar
Charlson Comorbidity Index (CCI)
Vascular-Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (V-POSSUM)
Preoperative Score to Predict Postoperative Mortality (POSPOM)

ABSTRACT

Background: Noncardiac vascular surgery (VS) patients have comorbidities that increase the risk of death after surgery. Assessing that risk is important to allocate the necessary resources and improve quality of care. We aimed to evaluate the incidence and predictors of 30-day post-operative mortality (POM) after VS and compare the performance of existing risk scores.

Materials and methods: Prospective cohort study including consecutive patients submitted to elective VS at a tertiary university hospital. We collected patients' demographics/perioperative data and calculated Surgical Apgar, age-adjusted Charlson Comorbidity Index (CCI), Vascular-Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (V-POSSUM) and Preoperative Score to Predict Postoperative Mortality (POSPOM). We performed multivariate logistic regression to assess independent factors with Odds Ratio (OR) and 95% confidence interval (CI) calculation and Cox-regression for time-to-event analysis. We tested the predictive ability of the scores using the area under ROC curve (AUROC).

Results: POM was 6.2% (n = 19/306), not different from expected by V-POSSUM (6.5%) or POSPOM (5.6%). Post-operative myocardial infarction (MI) and acute kidney injury (AKI) were associated with higher POM (OR 4.8, p = 0.011 and OR 5.4, p = 0.001, respectively). On multivariate analysis, Chronic kidney disease (CKD) (OR 4.0, p = 0.021), Age (OR 1.1, p = 0.002), Peripheral arterial disease (PAD) (OR 8.0, p = 0.006), intra-operative red blood cells (RBC) Transfusion (OR 1.9, p < 0.001) and Atrial fibrillation (OR 8.4, p = 0.002) were considered independent predictors of POM (CAPTA score). The AUROC of our model was 0.882, better V-POSSUM (0.858), POSPOM (0.784), CCI (0.732) or Surgical Apgar (0.649).

Conclusion: Observed POM was similar to predicted by V-POSSUM or POSPOM. Age, PAD, CKD, atrial fibrillation and intraoperative RBC transfusion were independent risk factors for POM. Score V-POSSUM performed better than POSPOM, CCI or Surgical Apgar.

1. Introduction

Noncardiac vascular surgery (VS) may represent 0.5–2% of the surgeries performed worldwide [1,2]. The evolution of anesthetic/surgical techniques, perioperative planning and monitoring decreased the intraoperative mortality [3]. Nevertheless, postoperative mortality (POM) is still relevant: 4% before hospital discharge and 5.5% in the first year [4,5]. The probability of death increases with age, major/emergent surgery, severe coexisting diseases or postoperative complications [6–9]. Attentive perioperative care, close monitoring and early detection of complications may contribute to mortality reduction [6,7,10]. Risk estimation is important to adequate perioperative care to the individual patient and procedure.

Hospital mortality estimation by Simplified Acute Physiology Score (SAPS) or Acute Physiology and Chronic Health Evaluation (APACHE) after Intensive Care Unit (ICU) stay has produced good results [11–13]. However, these scores are not so useful for post-surgical patients since they focus on the severity of illness at admission [14]. The Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (POSSUM), from the United Kingdom, estimates 30-day

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https://doi.org/10.1016/j.ijsu.2019.12.010
Received 19 August 2019; Received in revised form 20 November 2019; Accepted 2 December 2019
Available online 14 December 2019
1743-9191/

mortality and morbidity after surgery using 12 pre and 6 intraoperative variables, making it difficult to use in preoperative planning and risk estimation [15,16]. The Portsmouth modification of POSSUM (P-POSSUM) improved its predictive ability and there is a variant specifically for VS patients, the Vascular POSSUM (V-POSSUM) with satisfactory performance [15,16].

The Preoperative Score to Predict Postoperative Mortality (POSPOM), from France, resulted in excellent estimation using 17 preoperative variables but its derivation cohort included many types of surgery [17]. The Surgical Apgar Score includes only 3 intraoperative variables and is being used in noncardiac surgery with acceptable results. Age-adjusted Charlson Comorbidity Index (CCI) estimates the 10-year mortality according to patients' comorbidities. American College of Surgeons National Surgical Quality Improvement Program score to predict post-operative mortality is available online, including a subset for use in VS, but they did not publish the equation making it unsuitable for clinical research [18,19]. Assessing the mortality risk before VS is of paramount importance to allocate the necessary resources and improve the quality of care.

In this study, we aimed to evaluate the incidence and predictors of POM after VS and compare which risk scores perform better in a Portuguese population.

2. Material and methods

2.1. Study design, setting and participants

Prospective observational cohort study including all adult consecutive patients submitted to elective arterial VS from January to April 2015 at a tertiary university hospital. We estimated to include 300 patients during the study period. Hypothesis was planned before analyzing data; exposures and outcomes were previously defined. This protocol was submitted to the institutional ethics committee (local reference CES 04–15) who approved the study. The protocol is also registered in ClinicalTrials.gov with the identifier NCT04051749. This manuscript has been reported in line with Strengthening the Reporting of Cohort Studies in Surgery (The STROCSS Statement) [20].

2.2. Data collection and outcomes

We prospectively collected preoperative: age, gender, weight, medical history, usual medication, vital signs, laboratory results, electrocardiographic findings, American Society of Anesthesiology (ASA) physical status; and intraoperative variables: type and duration of surgery/anesthesia, vital signs, drug administration, estimated blood loss and transfusion requirements. Preoperative cardiac evaluation was mainly clinical: symptoms, medical history, functional capacity, dyspnea/orthopnea, usual medication. Further evaluation by echocardiography, cardiac stress test, coronary angiography, cardiac magnetic resonance was dependent on symptoms or laboratory analysis (Brain Natriuretic Peptide, troponins, arterial blood gas). Patients with coronary heart disease were included in the study only if their condition was stable (recent ischemic pain more intense or longer duration than usual, caused by less effort or occurring at rest were referred to the Cardiology Department). In addition, patients with heart failure and worsening symptoms, higher BNP or lower ejection fraction than basal were referred to the Cardiology Department. We defined Chronic Kidney Disease (CKD) as estimated glomerular filtration rate (Creatinine Clearance by Cockcroft-Gault equation) less than 60 ml/min. Surgeries were divided into intermediate or high-risk according to the joint guidelines of European Society of Cardiology (ESC) and European Society of Anesthesiology (ESA) [21]. Post-operative records included vital signs, laboratory results, major cardiovascular events (stroke, acute myocardial infarction defined as chest pain, electrocardiographic ST variations or a rise in troponin superior to 0.034 ng/ml in the first 72 h after surgery, *de novo* atrial fibrillation or heart failure including pulmonary edema, ventricular fibrillation or cardiac arrest, complete heart block), renal complications (acute kidney injury as defined by the Acute Kidney Injury Network criteria [22] or end-up in dialysis). We analyzed length of stay (LOS) and 30-day POM. We calculated Surgical Apgar, CCI, V-POSSUM and POSPOM.

2.3. Statistical analysis

We used descriptive statistics to summarize the data. We performed Kolmogorov-Smirnov test and Histogram analysis to assess normality of data and we selected parametric (independent samples *t*-test) or non-parametric tests (Mann-Whitney-U) accordingly. To compare proportions between groups in univariate analysis we used the Chi-square test. We determined independent predictors of postoperative mortality using multivariate logistic regression with forward conditional method, calculating Odds Ratio (OR) and its 95% confidence interval (CI). Variables with $p < 0.05$ in the univariate analysis were included in the multivariate analysis. We created a model using the adjusted OR of the independent variables as scoring points and analyzed the Area Under Receiver Operating Characteristics curve (AUROC) of the different risk indexes to measure their predictive discrimination. We used the Hosmer-Lemeshow test to determine the goodness of fit of our model (calibration), $p > 0.05$ for no significant difference between predictive model and observed data. To reduce the potential of overfitting we selected the leave-one-out cross-validation approach and the bootstrapping method (n = 1000 samples). We also analyzed time-to-event using Cox-proportional hazards ratio. We used Stata 14 and SPSS 25 to analyze the data.

3. Results

We included all 306 patients submitted to elective arterial VS during the study period, 129 being intermediate and 177 high-risk surgery. All-cause 30-day POM was 6.2% (n = 19), not different ($p > 0.05$) from expected by V-POSSUM (6.5%) or POSPOM (5.6%). Table 1 displays univariate analysis of POM. Aortic surgery (10%) was less common than lower limb (78%) or carotid surgery (12%) and had a significant higher mortality, 9.5% vs. 6.8% vs. 0%, respectively ($p < 0.001$). Endovascular approach represented 20.1% of surgeries and had the same mortality as open surgery (6.2%, $p = 0.773$). The incidence of post-operative cardiovascular events was 6.2% and renal complications 15.4%, both associated with higher POM: OR 4.8 (1.4–16.4, $p = 0.011$) and OR 5.4 (2.1–14.1, $p = 0.001$), respectively.

Table 2 shows the scores of the different risk models. All listed scores were significantly higher ($p < 0.001$) in the mortality group. Table 3 contains the multiple logistic and cox-regression used to assess the effect of variables on POM. Chronic kidney disease (CKD), Age, Peripheral arterial disease (PAD), intraoperative red blood cells (RBC) Transfusion and Atrial fibrillation (CAPTA score) were considered independent predictors of POM, although more significant in logistic than in cox-regression. Model points were based on the OR values for these factors, rounded to the nearest whole number. To include age in our model, we transformed it into a categorical variable and considered 3 points for each decade after 40 years, resulting in 3–18 model points (Table 4). Predictive ability remained the same after this transformation.

Fig. 1 presents graphically the AUROC of the best risk models. Our CAPTA score had an AUROC of 0.882 with a Hosmer-Lemeshow test for the goodness of fit of 0.66. If using only preoperative variables (without RBC intraoperative transfusion) the AUROC is 0.833 with a Hosmer-Lemeshow test of 0.15. Using the leave-one-out cross-validation approach and the bootstrap analysis (with the intraoperative variable) resulted in the same AUROC: 0.881. Table 4 represents the AUROC with 95% CI of V-POSSUM was 0.858, POSPOM was 0.784, CCI was 0.732 and Surgical Apgar was 0.649. Using physiologic POSSUM (only preoperative variables) resulted in an AUROC of 0.855. Unadjusted CCI

Table 1
Univariate analysis of 30-day mortality.

Variables	Mortality group n = 19	Survival group n = 287	p value
Age (years), median [IQR]	77 [65–82]	65 [58–74]	**0.001**[a]
Male gender, n(%):	11 (57.9)	204 (71.1)	0.298[b]
Prior medical history, n(%):			
Arterial Hypertension	16 (84.7)	204 (71.3)	0.341[b]
Peripheral Arterial Disease	15 (78.9)	157 (54.9)	**0.050**[b]
Chronic Kidney Disease	13 (68.4)	87 (30.4)	**0.001**[b]
Current Smoker	9 (47.4)	124 (43.4)	0.733[b]
Diabetes Mellitus	7 (36.8)	156 (54.5)	0.134[b]
Congestive Heart Failure	7 (36.8)	33 (11.5)	**0.002**[b]
Cerebrovascular Disease	4 (21.1)	59 (20.6)	1.000[c]
Coronary Disease	4 (21.1)	15 (5.2)	**0.023**[c]
Atrial fibrillation	6 (31.6)	13 (4.5)	< **0.001**[b]
Dependent functional status, n (%)	5 (26.3)	22 (7.7)	**0.006**[b]
ASA physical status, II/III n(%) IV	15 (78.9) 4 (21.1)	267 (93.7) 18 (6.3)	**0.039**[c]
Usual medication, n(%):			
Antiplatelet drug	14 (73.7)	179 (62.9)	0.331[b]
Diuretic	12 (63.2)	87 (30.4)	**0.003**[b]
Statin	9 (47.4)	180 (62.9)	0.176[b]
Beta-Blocker	8 (42.1)	68 (23.8)	0.074[b]
Insulin	3 (15.8)	76 (26.6)	0.299[c]
Pre-op lab results, median [IQR]:			
Hemoglobin (g/dL)	11.9 [10.3–13.8]	11.3 [9.6–12.7]	0.327[a]
Serum Creatinine (mg/dL)	1.7 [0.9–3.2]	0.9 [0.7–1.4]	**0.001**[a]
Serum Urea (mg/dL)	78 [58–91]	41 [30–63]	< **0.001**[a]
[Na^+] mEq/L	135 [133–139]	137 [135–140]	**0.035**[a]
[K^+] mEq/L	4.0 [3.5–4.5]	4.4 [4.0–4.8]	**0.033**[a]
[Cl^-] mEq/L	101 [99–107]	102 [99–105]	0.836[a]
Blood glucose (mg/dl)	96 [89–109]	116 [92–170]	0.099[a]
Intra-operative variables:			
High-risk surgery, n(%)	12 (63.2)	165 (57.5)	0.628[b]
Endovascular surgery	4 (6.2)	60 (20.9)	0.773[c]
General anesthesia, n (%)	6 (31.6)	83 (28.9)	0.805[b]
Surgery duration (h), median [IQR]	1.5 [0.5–4.0]	2.2 [1.0–3.0]	0.521[a]
Min HR (bpm), median [IQR]	72 [56–81]	61 [53–70]	**0.038**[a]
Min MAP (mmHg), median [IQR]	72 [62–81]	73 [60–89]	0.514[a]
RBC transfused units median [IQR]	1 [0–1]	0 [0-0]	**0.049**[a]
Post-operative AMI, n(%)	4 (21.1)	15 (5.2)	**0.023**[c]
Post-operative AKI, n(%)	11 (57.9)	58 (20.2)	**0.001**[b]

ASA - American Society of Anesthesiology | HR - Heart Rate | MAP - Mean Arterial Pressure |
AMI - Acute Myocardial Infarction | AKI - Acute Kidney Injury.
[a] Mann-Whitney test.
[b] Chi-square test.
[c] Fisher's-exact test. IQR: Interquartile range [P25–P75].

Table 2
Comparison of risk scores to predict mortality.

Risk scores	Mortality group n = 19	Survival group n = 287	p value
Surgical Apgar, median [IQR]	3 [2–5]	5 [3–6]	< **0.001***
Charlson Comorbidity index, median [IQR]	9 [5–10]	6 [4–8]	< **0.001***
V-POSSUM, median [IQR]	47 [40–51]	34 [30–40]	< **0.001***
POSPOM, median [IQR]	35 [30–38]	29 [27–32]	< **0.001***

* Mann-Whitney test. IQR: Interquartile range [P25–P75]. V-POSSUM: Vascular-Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity. POSPOM: Preoperative Score to Predict Postoperative Mortality.

results in an AUROC of 0.638.

4. Discussion

Observed POM was not different from that expected by V-POSSUM or POSPOM. Age has been associated with postoperative mortality and that may be the reason why many scores include this parameter [5,8,23]. Not surprisingly, age-adjusted CCI performed better (0.732) than unadjusted CCI (0.638). Although not derived for POM prediction, CCI is useful after VS because this population have many comorbidities that increase the risk of death, irrespective of the surgery performed.

Regarding PAD, evidence suggests that it could be a surrogate for cardiac disease [24,25]. Ankle-Brachial Index (leg divided by arm blood pressure) is helpful in the diagnosis of PAD and was recently related to mortality [24,25]. Chronic kidney disease is another comorbidity frequently implicated in mortality [26]. Both PAD and CKD were independent risk factors for POM in our study together with atrial fibrillation. Association of cardiac arrhythmia and mortality after cardiac surgery has been previously stablished [27,28]. To our knowledge, this association was not described after VS, however, we believe that this association is possible since VS and cardiac surgery patients share many cardiovascular comorbidities.

At least two studies report an association between intraoperative RBC transfusions and postoperative mortality and morbidity after VS [29,30]. It was also an independent risk factor for POM in our study. Patients who developed postoperative cardiovascular or renal complications had higher mortality. This has been extensively studied in the past and evidence support these results [31–35].

The POSSUM score consists of 12 physiologic and 6 intraoperative variables. Predictive ability of POSSUM improved with the Portsmouth modification and subdividing it for different surgeries (vascular, colorectal, esophagogastric). It was the best score to predict POM after VS even when using only the 12 physiologic variables. The POSPOM was derived and validated using many types of noncardiac surgery and so, it is not surprising that it performed a little worse than POSSUM. However, it has the advantage of only using preoperative variables and tries to differentiate the surgical specialty by adding more points according to the surgical risk. We believe it is also a good option to use in this situation.

The strengths of CAPTA score are its simplicity (only five clinical variables required), derived using all types of elective VS (broader/easier application) and time-to-event ponderation. The disadvantages are that it includes an intraoperative variable (RBC transfusion) and was derived using 300 patients from one hospital. The main limitation of our study is not having the cause of mortality and the relative short follow-up. In addition, our sample covers only elective VS but we believe that including more than a 1/3 of the annual VS (number of surgeries decrease in summer) is a fair sample size.

5. Conclusion

In conclusion, observed POM was similar to that predicted by V-POSSUM or POSPOM. Post-operative MI or AKI increased the risk of death. Age, PAD, CKD, atrial fibrillation and intraoperative RBC transfusion were independent risk factors for POM. Score V-POSSUM performed better than POSPOM, CCI or Surgical Apgar even when using only the physiologic variables.

Ethical approval

The institutional ethics committee approved the study protocol (CES 04–15) and patients signed the informed consent form to participate.

Sources of funding

No funds were needed.

Table 3
Multivariate analysis of mortality predictors.

Variables	OR (95%CI)	p value	Adjusted OR (95%CI)	p value	Model points	Adjusted HR (95%CI)	p value
Age	1.1 (1.0–1.1)	0.001	1.1 (1.0–1.2)	0.002		1.06 (1.0–1.12)	0.050
Age by decade[a]	2.5 (1.5–4.1)	< 0.001	3.1 (1.7–5.8)	< 0.001	3–18[a]	2.0 (1.2–3.3)	0.010
Peripheral Arterial Disease	3.1 (1.0–9.5)	0.05	8.0 (1.8–34.9)	0.006	8	3.9 (0.98–15.8)	0.052
Chronic Kidney Disease	5.1 (1.8–13.5)	0.002	4.0 (1.2–12.9)	0.021	4	3.9 (1.1–13.3)	0.032
Congestive Heart Failure	4.5 (1.6–12.2)	0.003					
Dependent functional status	4.3 (1.41–13.0)	0.01					
ASA-PS IV vs II/III	4.0 (1.2–13.2)	0.025					
Atrial fibrillation	9.7 (3.2–29.6)	< 0.001	8.4 (2.1–33.1)	0.002	8	5.4 (1.8–16.4)	0.003
Diuretic chronic medication	3.9 (1.5–10.3)	0.006					
Intraop RBC transfusion	1.4 (1.1–1.9)	0.018	1.9 (1.4–2.6)	< 0.001	2	1.7 (1.2–2.3)	0.001
Post-operative AMI	4.8 (1.4–16.4)	0.011					
Post-operative AKI	5.4 (2.1–14.1)	0.001					

OR – Odds Ratio. | HR – Hazards Ratio. | ASA-PS: American Society of Anesthesiology-Physical Status | Intraop RBC – Intraoperative Red Blood Cells transfusion | AMI – Acute Myocardial Infarction | AKI – Acute Kidney Injury.
[a] 3 points for each decade after 40 years (age 40–49: 3; 50–59: 6; 60–69: 9; 70–79: 12; 80–89: 15; ≥90: 18 points).

Table 4
Area Under Receiver Operating Characteristics Curve and the 95% Confidence Interval of the different scores.

	AUROC	95% CI
CAPTA	0.882	0.809 –0.981
V-POSSUM	0.858	0.797–0.933
POSPOM	0.784	0.662–0.907
CCI	0.732	0.601–0.863
Surgical Apgar	0.649	0.491–0.804

AUROC: Area Under Receiver Operating Characteristics Curve. CAPTA: Chronic kidney disease, Age, Peripheral arterial disease, intraoperative red blood cell Transfusion, Atrial fibrillation. CI: Confidence Interval. V-POSSUM: Vascular-Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity. POSPOM: Preoperative Score to Predict Postoperative Mortality. CCI: Charlson Comorbidity Index.

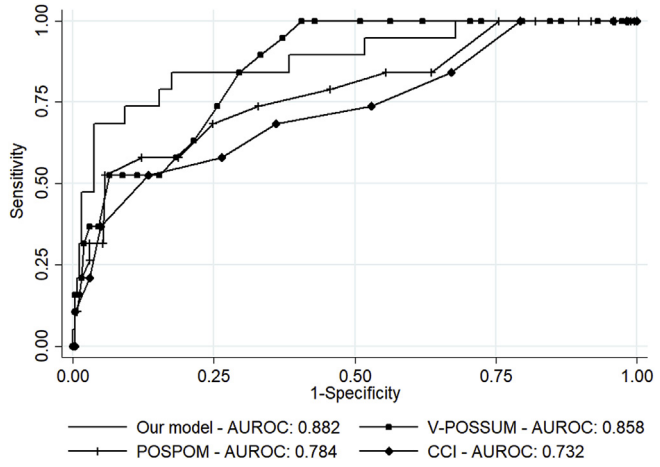

Fig. 1. eceiver Operating Characteristic (ROC) curve of the risk scores.
V-POSSUM: Vascular-Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity. POSPOM: Preoperative Score to Predict Postoperative Mortality. CCI: age-adjusted Charlson Comorbidity Index. AUROC: Area Under ROC curve

Author contribution

Pedro Reis and Fernando Abelha were responsible for study design. All authors contributed to data collection and analysis. Pedro Reis and Fernando Abelha supervised the team and wrote the manuscript.

Research registration number

Name of the registry: Clinicaltrials.gov.
Unique Identifying number or registration ID: ClinicalTrials.gov Identifier: NCT04051749.
Hyperlink to the registration (must be publicly accessible): https://clinicaltrials.gov/ct2/show/NCT04051749.

Guarantor

Pedro Reis.

Provenance and peer review

Not commissioned, externally peer-reviewed.

CRediT authorship contribution statement

Pedro Reis: Formal analysis, Writing - original draft. **Fernando Abelha:** Writing - review & editing.

Declaration of competing interest

All authors have nothing to declare.

Acknowledgements

All authors were involved in data collection. Pedro Reis was responsible for data analysis and manuscript writing. Fernando Abelha coordinated the project and revised the manuscript. All authors approved the final version of the manuscript.

List of abbreviations

AKI	acute kidney injury
APACHE	Acute Physiology and Chronic Health Evaluation
ASA	American Society of Anesthesiology
AUROC	Area Under Receiver Operating Characteristics curve
CAPTA	Chronic kidney disease, Age, Peripheral arterial disease, intraoperative red blood cell Transfusion, Atrial fibrillation
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CKD	Chronic kidney disease
ESA	European Society of Anesthesiology
ESC	European Society of Cardiology
ICU	Intensive Care Unit
LOS	length of stay

MI myocardial infarction
OR Odds Ratio
PAD Peripheral Arterial Disease
POM post-operative mortality
POSPOM Preoperative Score to Predict Postoperative Mortality
RBC Red Blood Cells
SAPS Simplified Acute Physiology Score
STROCSS Strengthening the Reporting of Cohort Studies in Surgery
V-POSSUM Vascular-Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity
VS Noncardiac Vascular Surgery

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.12.010.

References

[1] T.G. Weiser, S.E. Regenbogen, K.D. Thompson, A.B. Haynes, S.R. Lipsitz, W.R. Berry, et al., An estimation of the global volume of surgery: a modelling strategy based on available data, Lancet 372 (9633) (2008) 139–144.
[2] P.K. Gupta, H. Gupta, A. Sundaram, M. Kaushik, X. Fang, W.J. Miller, et al., Development and validation of a risk calculator for prediction of cardiac risk after surgery, Circulation 124 (4) (2011) 381–387.
[3] H. Ohlsson, O. Winso, Assessment of the surgical Apgar score in a Swedish setting, Acta Anaesthesiol. Scand. 55 (5) (2011) 524–529.
[4] R.M. Pearse, R.P. Moreno, P. Bauer, P. Pelosi, P. Metnitz, C. Spies, et al., Mortality after surgery in Europe: a 7 day cohort study, Lancet 380 (9847) (2012) 1059–1065.
[5] T.G. Monk, V. Saini, B.C. Weldon, J.C. Sigl, Anesthetic management and one-year mortality after noncardiac surgery, Anesth. Analg. 100 (1) (2005) 4–10.
[6] S.F. Khuri, W.G. Henderson, R.G. DePalma, C. Mosca, N.A. Healey, D.J. Kumbhani, et al., Determinants of long-term survival after major surgery and the adverse effect of postoperative complications, Ann. Surg. 242 (3) (2005) 326–341.
[7] A.A. Ghaferi, J.D. Birkmeyer, J.B. Dimick, Variation in hospital mortality associated with inpatient surgery, N. Engl. J. Med. 361 (14) (2009) 1368–1375.
[8] R.M. Pearse, D.A. Harrison, P. James, D. Watson, C. Hinds, A. Rhodes, et al., Identification and characterisation of the high-risk surgical population in the United Kingdom, Crit. Care 10 (3) (2006) R81.
[9] F.J. Abelha, M.A. Castro, N.M. Landeiro, A.M. Neves, C.C. Santos, Mortality and length of stay in a surgical intensive care unit, Rev. Bras. Anestesiol. 56 (1) (2006) 34–45.
[10] B.L. Hall, B.H. Hamilton, K. Richards, K.Y. Bilimoria, M.E. Cohen, C.Y. Ko, Does surgical quality improve in the American college of surgeons national surgical quality improvement Program: an evaluation of all participating hospitals, Ann. Surg. 250 (3) (2009) 363–376.
[11] W.A. Knaus, E.A. Draper, D.P. Wagner, J.E. Zimmerman, Apache II: a severity of disease classification system, Crit. Care Med. 13 (10) (1985) 818–829.
[12] J.L. Vincent, R. Moreno, Clinical review: scoring systems in the critically ill, Crit. Care 14 (2) (2010) 207.
[13] J.R. Le Gall, S. Lemeshow, F. Saulnier, A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study, Jama 270 (24) (1993) 2957–2963.
[14] N.A. Halpern, S.M. Pastores, R.J. Greenstein, Critical care medicine in the United States 1985-2000: an analysis of bed numbers, use, and costs, Crit. Care Med. 32 (6) (2004) 1254–1259.
[15] D. Mosquera, N. Chiang, R. Gibberd, Evaluation of surgical performance using V-POSSUM risk-adjusted mortality rates, ANZ J. Surg. 78 (7) (2008) 535–539.
[16] K. Mohammedi, L. Potier, N. Belhatem, N. Matallah, S. Hadjadj, R. Roussel, et al., Lower-extremity amputation as a marker for renal and cardiovascular events and mortality in patients with long standing type 1 diabetes, Cardiovasc. Diabetol. 15 (2016) 5.
[17] Y. Le Manach, G. Collins, R. Rodseth, C. Le Bihan-Benjamin, B. Biccard, B. Riou, et al., Preoperative score to predict postoperative mortality (POSPOM): derivation and validation, Anesthesiology 124 (3) (2016) 570–579.
[18] Y. Liu, M.E. Cohen, C.Y. Ko, K.Y. Bilimoria, B.L. Hall, Considerations in releasing equations for the American college of surgeons NSQIP surgical risk calculator: in reply to Wanderer and Ehrenfeld, J. Am. Coll. Surg. 223 (4) (2016) 674–675.
[19] K.Y. Bilimoria, Y. Liu, J.L. Paruch, L. Zhou, T.E. Kmiecik, C.Y. Ko, et al., Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons, J. Am. Coll. Surg. 217 (5) (2013) 833–842.
[20] R.A. Agha, M.R. Borrelli, M. Vella-Baldacchino, R. Thavayogan, D.P. Orgill, for the STROCSS Group, The STROCSS statement: strengthening the reporting of cohort studies in surgery, Int. J. Surg. 46 (2017) 198–202.
[21] S.D. Kristensen, J. Knuuti, A. Saraste, S. Anker, H.E. Botker, S. De Hert, et al., ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: the Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA), Eur. J. Anaesthesiol. 31 (10) (2014) 517–573 2014.
[22] R.L. Mehta, J.A. Kellum, S.V. Shah, B.A. Molitoris, C. Ronco, D.G. Warnock, et al., Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury, Crit. Care 11 (2) (2007) R31.
[23] C. Naughton, R.O. Feneck, The impact of age on 6-month survival in patients with cardiovascular risk factors undergoing elective non-cardiac surgery, Int. J. Clin. Pract. 61 (5) (2007) 768–776.
[24] A. Velescu, A. Clara, R. Marti, R. Ramos, S. Perez-Fernandez, L. Marcos, et al., Abnormally high ankle-brachial Index is associated with all-cause and cardiovascular mortality: the REGICOR study, Eur. J. Vasc. Endovasc. Surg. 54 (3) (2017) 370–377.
[25] E.J. Hendriks, J. Westerink, P.A. de Jong, G.J. de Borst, H.M. Nathoe, W.P. Mali, et al., Association of high ankle brachial Index with incident cardiovascular disease and mortality in a high-risk population, Arterioscler. Thromb. Vasc. Biol. 36 (2) (2016) 412–417.
[26] J.X. Xie, T.J. Glorioso, P.B. Dattilo, V. Aggarwal, P.M. Ho, A.E. Barón, et al., Effect of chronic kidney disease on mortality in patients who underwent lower extremity peripheral vascular intervention, Am. J. Cardiol. 119 (2017) 669–674.
[27] D. Anghel, R. Anghel, F. Corciova, M. Enache, G. Tinica, Preoperative arrhythmias such as atrial fibrillation: cardiovascular surgery risk factor, BioMed Res. Int. 2014 (2014) 584918.
[28] W.T. O'Neal, J.T. Efird, S.W. Davies, Y.M. Choi, C.A. Anderson, L.C. Kindell, et al., Preoperative atrial fibrillation and long-term survival after open heart surgery in a rural tertiary heart institute, Heart Lung : J. Crit. Care 42 (6) (2013) 442–447.
[29] S.D. O'Keefe, D.L. Davenport, D.J. Minion, E.E. Sorial, E.D. Endean, E.S. Xenos, Blood transfusion is associated with increased morbidity and mortality after lower extremity revascularization, J. Vasc. Surg. 51 (2010) 616–621.
[30] T.M. Valentijn, S.E. Hoeks, E.J. Bakker, K.M. van de Luijtgaarden, H.J. Verhagen, R.J. Stolker, et al., The impact of perioperative red blood cell transfusions on postoperative outcomes in vascular surgery patients, Ann. Vasc. Surg. 29 (3) (2015) 511–519.
[31] A.M. O'Hare, A.N. Sidawi, J. Feinglass, K.M. Merine, J. Daley, S. Khuri, et al., Influence of renal insufficiency on limb loss and mortality after initial lower extremity surgical revascularization, J. Vasc. Surg. 39 (2004) 709–716.
[32] A.D. Opprea, F.W. Lombard, W.W. Liu, W.D. White, J.A. Karhausen, T.E. Miller, et al., Baseline pulse pressure, acute kidney injury, and mortality after noncardiac surgery, Anesth. Analg. 123 (6) (2016) 1480–1489.
[33] P. Arora, S. Davari-Farid, L. Pourafkari, A. Gupta, H.H. Dosluoglu, N.D. Nader, The effect of acute kidney injury after revascularization on the development of chronic kidney disease and mortality in patients with chronic limb ischemia, J. Vasc. Surg. 61 (2015) 720–727.
[34] M. Huber, T. Ozrazgat-Baslanti, P. Thottakkara, P.A. Efron, R. Feezor, C. Hobson, et al., Mortality and cost of acute and chronic kidney disease after vascular surgery, Ann. Vasc. Surg. 30 (2016) 72–81.
[35] M. Huber, T. Ozrazgat-Baslanti, P. Thottakkara, S. Scali, A. Bihorac, C. Hobson, Cardiovascular-specific mortality and kidney disease in patients undergoing vascular surgery, JAMA Surg 151 (5) (2016) 441–450.

7. Discussion

7.1 Main results and considerations

In all our papers, the incidence of mortality, MACE and AKI after VS was within the predicted range of previous studies. Postoperative complications increased the risk of other adverse events or mortality and extended the LOS. Age, IHD, atrial fibrillation, diabetes mellitus, CKD, peripheral arterial disease (PAD), active smoking, surgery duration or risk were some of the independent risk factors found. Patients with adverse outcomes after VS had higher scores in the tested models. Surgical scores performed better than ICU severity of illness models.

Our studies comply with Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines.[62]

7.2 Mortality

Postoperative 30-day mortality after Endovascular Aneurysm Repair (EVAR) was 2% (Paper A). The ESC/ESA guidelines consider EVAR as an intermediate risk surgery with a 30-day mortality risk of 1-5%.[17] Some of the first cases performed at the institution were included which corresponded to the beginning of the learning curve of the technique. However, these cases did not seem to have a negative impact on the results. Since we only had two cases of mortality, we decided not to perform multivariate logistic regression.

Hospital mortality in patients admitted at a surgical ICU after VS was 5% (1.3% after intermediate and 8.4% after high-risk surgery), half of them occurring during ICU stay (Paper B). Mortality was higher in patients developing MACE or AKI after surgery ($p<0.001$). After multivariate logistic regression, age, active smoking, high-risk surgery, serum sodium, urea and leukocyte count at ICU admission were considered independent risk factors while hematocrit after surgery was considered a protective factor. In this study, we included postoperative factors in order to have a fair comparison with the ICU risk scores that are calculated 24h after admission. This resulted in an excellent AUROC (0.86) even after bootstrapping and leave-one-out cross-validation.

Postoperative 30-days mortality after elective VS was 6% (Paper D). The proportion of patients submitted to high-risk surgery was higher in paper D than B and is a factor that can explain the higher mortality. There are several ICUs at our hospital and the surgical ICU may not receive all high-risk surgery. Most VS, except for asymptomatic carotid endarterectomy (CEA), is intermediate or high-risk surgery. Furthermore, patients undergoing VS have many comorbidities that increase the risk of death, regardless of the surgery performed. In paper D, age, PAD, CKD, atrial fibrillation and intraoperative Red Blood Cell (RBC) transfusion were independent risk factors for mortality. The leave-one-out cross-validation approach and the bootstrap analysis (with the intraoperative variable) resulted in the same AUROC: 0.88. If using only preoperative variables (without RBC intraoperative transfusion), the AUROC was 0.83. This means that intraoperative parameters such as RBC transfusion may be considered when estimating the risk of mortality.

The ICU models SAPS and APACHE are similar except for Blood Pressure (BP) (SAPS uses systolic BP and APACHE uses mean BP), renal function assessment (SAPS covers urinary output and APACHE just laboratory results), SAPS includes bilirubin while APACHE contains respiratory rate and hematocrit. In paper B, they had a comparable performance (AUROC 0.75 vs 0.77), respectively. Both SAPS and APACHE anticipate admission after surgery in the scoring system; however, they performed worse than the surgical scores POSPOM (0.80) and V-POSSUM (0.83). In face of these results, surgical risk scores should substitute ICU models in admissions after surgery.[63]

In paper D, we were able to register prospectively the intraoperative parameters necessary to calculate the total V-POSSUM. However, there was no difference between the total (AUROC 0.858) and the physiologic POSSUM only (AUROC 0.855). It is not very surprising since the equation for V-POSSUM is different from the P-POSSUM but the surgical variables of the score are not focused in VS. Presence of malignancy and soiling contamination are not an adequate fit in VS, this last one especially nowadays with the growing number of endovascular procedures in abdominal aorta. Likewise, because we included only elective VS, we lost the discrimination ability of the type of admission included in the model. Even though, V-POSSUM was the best score to predict postoperative mortality in both our studies, much like previous reports.[33,64-66]

In both papers B and D, the observed mortality was similar to predicted by POSPOM or V-POSSUM. In paper B, V-POSSUM predicted a hospital mortality of 5.3% (*n* = 44) resulting in an observed/expected ratio of 0.98 (43/44). In paper D, mortality prediction by V-POSSUM was 6.5% and by POSPOM 5.6%, similar to the 6.2% we observed. Applying the CAPTA score (from paper D) without RBC transfusion (not available) in the ICU patients resulted in an AUROC of 0.71. This emphasizes that risk models should be used in the context they were created and not generalized randomly.

7.3 Cardiac events

The causality between surgery and MI has some controversial topics. First, because time-to-event remains uncertain, the follow-up after surgery is not standard, varying from 3 to 7 days.[67] Second, postoperative raise in Troponins may be considered as MI or Myocardial Injury after Noncardiac Surgery (MINS). Third, studies can report MACE as MI or vice-versa.[42-44] Most widespread MACE are those described by Lee.[5]

In paper A, we defined MI as an increase in high-sensitivity troponin levels > 0.034 ng/mL in the first 72h after surgery, following the ESC/American College of Cardiology criteria.[61] Incidence of MI was 5%, the superior cutoff of ESC/ESA guidelines.[17] Postoperative AKI increased the risk of MI, adjusted OR 24.4. Incidence of MI after EVAR in the meta-analysis of Stather *et al*.[68] was 6.8% similar to 6.3% found in the meta-analysis of Thomas *et al*.[69]

In paper C, we observed 81 MACE (28 MI, 22 arrhythmias, 10 CPE, 9 AHF, and 12 cardiac arrest/death) in 60 patients, representing an incidence of 6.5% (3.3% after intermediate and 9.8% after high-risk surgery). Regarding type of admission, elective surgery had 5.9% MACE versus 12.3% after emergent surgery. We used the same definition for MI and the incidence was 3.0% (1.5% after intermediate and 4.6% after high-risk surgery). Previous history of IHD, atrial fibrillation, insulin-treated diabetes mellitus, mechanical ventilation, and heart rate at admission were considered independent predictors; some of this variables were also recently reported by Sutzko *et al*.[70] Having MACE increased the ICU LOS (44 [21–90] versus 21 [16–43] hours, p<0.001) and the risk of hospital mortality, OR 9.9, 95% Confidence Interval (CI) 5.0-19.9.

Medical history of atrial fibrillation, IHD, or insulin-treated diabetes mellitus have been previously identified as risk factors for MACE.[71] The last two are included in RCRI and VSG, whereas VQI and SAVS include all diabetic patients regardless of insulin use. The AUROC of RCRI (0.66) and VSG-CRI (0.69) were slightly worse than VQI-CRI (0.71) or SAVS-CRI (0.73), similar to previous studies.[72-78] We tested our independent predictors and we got an AUROC of 0.79. After leave-one-out cross-validation and bootstrapping, we obtained an AUROC of 0.77. However, we should notice that our score includes two postoperative variables. Removing them from the equation result in an AUROC of 0.71. Despite the five variants of VQI depending on the surgery performed, its AUROC was not much different from VSG or SAVS. When comparing our total model with the other scores, the *p* values were <.001 for RCRI, .002 for VSG-CRI, .0140 for VQI-CRI, and .0218 for SAVS-CRI. Applying our model to paper D database, we get an AUROC of 0.82. Excluding the two postoperative variables results in an AUROC of 0.74.

7.4 Other complications

In paper A, we obtained 18% incidence of AKI after EVAR, consistent with previous studies (9-29%).[56,79-81] After calculation of eGFR, we measured AKI with RIFLE criteria but the results were the same (one patient developed Stage 2 and all others Stage 1 AKI). Preoperative serum urea, general anesthesia and surgery duration were considered independent predictors of AKI in multivariate analysis. In a multicenter study, there were fewer systemic complications with local or regional than general anesthesia; however, these patients had more complex and longer procedures.[82] Another studies and a meta-analysis later confirmed this information both in elective and emergent EVAR.[83-85] Patients with AKI had longer LOS.

Our regression included postoperative variables and had an AUROC of 0.88. This compares to 0.72 of VSKIPS model 1 (preoperative) and 0.79 of VSKIPS model 2 (pre and intraoperative variables). We defined AKI based on the KDIGO classification whereas VSKIPS was based on AKIN criteria.[58] We had one variable in common with VSKIPS, procedure duration, which may indicate more complex surgery and more intravenous contrast, a known risk factor for AKI.[86-88] Unfortunately, it was not possible to collect the amount of contrast or AKI preventive strategies used in the perioperative period.

Excluding patients with CKD, incidence of AKI (AKIN criteria) in patients admitted to ICU after VS was 5.0% (4.1% in intermediate and 5.9% after high-risk surgery). After endovascular surgery, the incidence was 10.6%. Two previous studies report an incidence of 48-49%.[89,90] In addition to intravenous contrast, peri-renal manipulation or stent fixation, microembolization into kidney vasculature, accessory renal artery occlusion, inflammatory and ischaemic response after endovascular approach have been suggested to play a part.[54-56] Endovascular is considered less invasive than open surgery but surgical/anesthetic teams should be aware of the risk of AKI. Incidence of AKI in paper D database (excluding patients with CKD) was 9.8%. This may be explained because in this prospective study, we also considered the postoperative urinary output and acute RRT. These data will be the subject of future studies.

7.5 Strengths and limitations

Although papers B and C are retrospective in nature, the database was registered prospectively. Nevertheless, we should be aware that missing data or unrecorded variables might affect the results. Not all intraoperative information necessary to calculate the total V-POSSUM was available but it may not have influenced the results because some surgical variables are not designed for VS.

In paper D, we prospectively included all patients submitted to elective VS and followed them in many parts of hospital (ward, intermediate and intensive care). We tried to obtain the 3 months mortality; unfortunately, it was not possible in 30% of cases. We cannot exclude the possibility that some surgical complications may have affected the adverse outcomes we measured.

Regarding AKI, we could not collect the amount of contrast or AKI preventive strategies used during the procedure and the postoperative urinary output. This is the main reason why we still did not analyze this outcome.

We consider that using bootstrapping and cross validation is not ideal, however, it is an acceptable way to randomly test our scores. We performed time-to-event analysis and consider it important, even if no differences were found. Despite including some postoperative variables, we believe our models are simple and may be useful in different circumstances.

7.6 Future perspectives

General considerations

There is a lot that can be done in this field. The era of digital data has allowed associations between intraoperative events, such as vital signs or blood loss, and postoperative complications.[91] Adverse events after surgery may be used as a measurement of quality of care.[92] Besides mortality, MACE and AKI, important postoperative complications under study are pulmonary and surgical site infection.[93-95] High-risk patients will benefit from careful planning, prevention strategies or preoperative optimization.[96] They are also candidates for better intraoperative monitoring and longer follow-up since complications can arise up to 7 days after surgery.[97] Despite improvements in the knowledge of postoperative complications, we were still not able to reduce them significantly.[98] Research in cardiac surgery may be applied to VS as patients share many comorbidities. Surgical specialties are creating protocols for enhanced recovery after surgery (ERAS) to improve results.[99] Combination of scores or improving their predictive ability with minor changes may be another way to go.[100] Some of these strategies are described below.

Strategies to improve scores/ measurements /outcomes

Lee RCRI is the most extensively studied score to predict MACE after surgery. Its predictive ability improves if adjusting for age or using eGFR instead of the serum Creatinine cutoff. The protocol is registered in clinicaltrials.gov but the results are not yet available.[101] Calculation of eGFR using Cystatin-C instead of serum Creatinine produced better results.[102] Goal-directed fluid therapy to improve outcomes, serum or urinary biomarkers are also under study.[103-106] Glucose variability, lactate levels, hematocrit, hemoglobin or white blood cells count have been implicated in adverse events.[107-110] Other biomarkers such as high sensitivity C Reactive Protein, Copeptin, Survivin, Brain Natriuretic Peptide (BNP) are being used to early detect complications and improve the performance of risk scores.[110-115] Recombinant BNP successfully reduced complications after surgery with extracorporeal circulation.[116] Its role in other types of surgery remain to be seen.

Diagnosis of MI has improved with high sensitivity Troponins. Postoperative troponins have a linear relation with mortality, even if levels are <0.03 ng/ml.[117,118] Preoperative or variations between pre and postoperative troponins are also associated with mortality.[119] Three meta-analysis proved this relation in noncardiac surgery.[120-122] Frailty is also associated with perioperative mortality and MACE in noncardiac and vascular surgery.[123-132] Scales to measure it may be useful in preoperative assessment.

Future projects

First, I would like to publish the results regarding MACE after elective VS. I will also try to analyze the relation between surgical complications and adverse outcomes, namely, AKI. I will investigate the possibility of deriving a score using machine learning and compare the advantages and disadvantages of such method. I will try to validate the models in independent samples.

Second, I would like to do a systematic review and possible meta-analysis of mortality and MACE after VS. I already discussed this idea with a team of four that have published with such methodology in high impact journals.

Finally, I will like to share with anesthesiologists and surgeons the best strategies for preoperative assessment and possibly reduce postoperative complications. This might be used by giving to the patients the real informed consent and compare results between hospitals. It can also improve the logistic aspects of surgery and recovery.

8. Conclusions

The incidence of mortality, MACE and AKI in our papers was within the predicted range of previous studies. Perioperative adverse events increased the risk of other complications or mortality and extended the LOS. Assessing the risk is of paramount importance in an era where concerns about variations in the quality of care and use of healthcare resources are growing.

This thesis provides the most complete assessment and discussion of the current best evidence regarding risk scores to predict mortality and morbidity after VS. Worldwide, between 2 and 4 million VS are performed every year. We should be able to predict and treat perioperative complications that may affect 12% of these patients, a rate that may escalate in the future with increasing age and comorbidities. Preoperative evaluation is key but intra and postoperative monitoring should also be viewed as important. Targeted interventions to early detect and treat are mandatory to decrease the incidence and impact of these adverse events.

Anesthesiologists are usually present during all phases of perioperative care. They should know the impact of their practice in outcomes and know the best strategies to improve the results. Regular evaluation of adverse outcomes is important to ensure compliance with the best practice and current evidence.

To conclude, while some might recognize a PhD thesis as the end of a chapter in terms of individual scientific career, I believe it is the beginning of a journey. The ultimate goal is to produce clinical research to improve the outcomes and lives of patients submitted to VS.

9. References

1. Saklad M. Grading of Patients for Surgical Procedures. Anesthesiology 1941;2:281-4.
2. Dripps RD, Lamont A, Eckenhoff JE. The role of anesthesia in surgical mortality. JAMA 1961;178:261–6.
3. Mayhew D, Mendonca V, Murthy BVS. A review of ASA physical status - historical perspectives and modern developments. Anaesthesia 2019;74:373-9.
4. Goldman L, Caldera DL, Nussbaum SR, et al. Multifatorial Index of Cardiac Risk in noncardiac surgical procedures. NEJM 1977;297(16):845-50.
5. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and Prospective Validation of a Simple Index for Prediction of Cardiac Risk of Major Noncardiac Surgery. Circulation 1999;100:1043-49.
6. Knaus WA, Zimmerman JE, Wagner DP, Draper EA, Lawrence DE. APACHE II: a severity of disease classification system. Critical Care Medicine 1981;9(8):591-7.
7. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Critical Care Medicine 1985;13(10):818-29.
8. Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest 1991;100:1619-36.
9. Zimmerman JE, Kramer AA, McNair DS, Malila FM. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. Critical Care Medicine 2006;34:1297-310.
10. Le Gall JR, Loirat P, Alperovitch A, et al. A Simplified Acute Physiology Score for ICU patients. Critical Care Medicine 1984;12(11):975-7.
11. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA. 1993;270(24):2957-63.
12. Metnitz PG, Moreno RP, Almeida E, et al. SAPS 3--From evaluation of the patient to evaluation of the intensive care unit. Part 1: Objectives, methods and cohort description. Intensive Care Medicine 2005;31:1336-44.
13. Moreno RP, Metnitz PG, Almeida E, et al. SAPS 3--From evaluation of the patient to evaluation of the intensive care unit. Part 2: Development of a prognostic model for hospital mortality at ICU admission. Intensive Care Medicine 2005;31:1345-55.
14. Wirthlin DJ, Cambria RP. Surgery-Specific Considerations in the Cardiac Patient Undergoing Noncardiac Surgery. Progress in Cardiovascular Diseases 1998;40(5):453-68.
15. Glance LG, Lustik SJ, Hannan EL, et al. The Surgical Mortality Probability Model: derivation and validation of a simple risk prediction rule for noncardiac surgery. Ann Surg 2012;255:696-702.
16. Guay J, Choi P, Suresh S, Albert N, Kopp S, Pace NL. Neuraxial blockade for the prevention of postoperative mortality and major morbidity: an overview of Cochrane systematic reviews. Cochrane Database Syst Rev 2014:CD010108.
17. Kristensen SD, Knuuti J, Saraste A, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). Eur J Anaesthesiol 2014;31:517-73.
18. Morris CK, Ueshima K, Kawaguchi T, Hideg A, Froelicher VF. The prognostic value of exercise review of the literature. American Heart Journal 1991;122(5):1423-31.
19. Biccard BM. Relationship between the inability to climb two flights of stairs and outcome after major non-cardiac surgery: implications for the pre-operative assessment of functional capacity. Anaesthesia 2005;60:588–93.
20. Velescu A, Clara A, Cladellas M, et al. Anemia Increases Mortality After Open or Endovascular Treatment in Patients with Critical Limb Ischemia: A Retrospective Analysis. Eur J Vasc Endovasc Surg 2016;51:543-9.

21. Biccard BM, Scott DJA, Chan MTV, et al. Myocardial Injury After Noncardiac Surgery (MINS) in Vascular Surgical Patients: A Prospective Observational Cohort Study. Ann Surg 2018;268(2):357-63.
22. Ohlsson H, Winso O. Assessment of the Surgical Apgar Score in a Swedish setting. Acta Anaesthesiologica Scandinavica 2011;55:524-9.
23. Khuri SF, Henderson WG, DePalma RG, et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Ann Surg 2005;242:326-41.
24. Ghaferi AA, Birkmeyer JD, Dimick JB. Variation in hospital mortality associated with inpatient surgery. NEJM 2009;361:1368-75.
25. Pearse RM, Harrison DA, James P, et al. Identification and characterisation of the high-risk surgical population in the United Kingdom. Critical Care 2006;10:R81.
26. Abelha FJ, Castro MA, Landeiro NM, Neves AM, Santos CC. Mortality and length of stay in a surgical intensive care unit. Rev Bras de Anestesiol 2006;56:34-45.
27. Leung JM, Dzankic S. Relative importance of preoperative health status versus intraoperative factors in predicting postoperative adverse outcomes in geriatric surgical patients. Journal of the American Geriatrics Society 2001;49:1080-5.
28. Hall BL, Hamilton BH, Richards K, Bilimoria KY, Cohen ME, Ko CY. Does surgical quality improve in the American College of Surgeons National Surgical Quality Improvement Program: an evaluation of all participating hospitals. Ann Surg 2009;250:363-76.
29. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. Evaluation of outcome from intensive care in major medical centres. Ann Intern Med 1986:104(3):410-8.
30. Vincent JL, Moreno R. Clinical review: scoring systems in the critically ill. Critical Care 2010;14:207.
31. Keegan MT, Whalen FX, Brown DR, Roy TK, Afessa B. Acute Physiology and Chronic Health Evaluation (APACHE) III Outcome Prediction After Major Vascular Surgery. J Cardiothorac Vasc Anesth 2008;22(5):713-8.
32. Halpern NA, Pastores SM, Greenstein RJ. Critical care medicine in the United States 1985-2000: an analysis of bed numbers, use, and costs. Critical Care Medicine 2004;32:1254-9.
33. Mosquera D, Chiang N, Gibberd R. Evaluation of surgical performance using V-POSSUM risk-adjusted mortality rates. ANZ Journal of Surgery 2008;78:535-9.
34. Mohammedi K, Potier L, Belhatem N, et al. Lower-extremity amputation as a marker for renal and cardiovascular events and mortality in patients with long standing type 1 diabetes. Cardiovascular Diabetology 2016;15:5.
35. Copeland GP, Jones D, Walter M. POSSUM: a scoring system for surgical audit. Br J Surg 1991;78(3):355-60.
36. Prytherch DR, Whiteley MS, Higgins B, et al. POSSUM and Portsmouth POSSUM for predicting mortality. Br J Surg 1998;85:1217-20.
37. Le Manach Y, Collins G, Rodseth R, et al. Preoperative Score to Predict Postoperative Mortality (POSPOM): Derivation and Validation. Anesthesiology 2016;124:570-9.
38. Regenbogen SE, Ehrenfeld JM, Lipsitz SR, Greenberg CC, Hutter MM, Gawande AA. Utility of Surgical Apgar Score. Arch Surg 2009;144(1):30-6
39. Charlson ME, Pompei P, Ales KL, Mackenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987;40(5):373-83
40. Liu Y, Cohen ME, Ko CY, Bilimoria KY, Hall BL. Considerations in Releasing Equations for the American College of Surgeons NSQIP Surgical Risk Calculator: In Reply to Wanderer and Ehrenfeld. Journal of the American College of Surgeons 2016;223:674-5.
41. Bilimoria KY, Liu Y, Paruch JL, et al. Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons. Journal of the American College of Surgeons 2013;217:833-42.
42. Puelacher C, Lurati Buse G, Seeberger D, et al. Perioperative Myocardial Injury After Noncardiac Surgery: Incidence, Mortality, Characterization. Circulation 2018;137(12):1221-32.

43. Ollila A, Vikatmaa L, Virolainen J, et al. Perioperative Myocardial Infarction in Non-Cardiac Surgery Patients: A Prospective Observational Study. Scandinavian journal of surgery : SJS : official organ for the Finnish Surgical Society and the Scandinavian Surgical Society 2017;106:180-6.
44. Liem VGB, Hoeks SE, Grune F, et al. Prognostic value of postoperative high-sensitivity troponin T in patients with different stages of kidney disease undergoing noncardiac surgery. Br J Anaesth 2018;120:84-93.
45. Liu JB, Liu Y, Cohen ME, Ko CY, Sweitzer BJ. Defining the Intrinsic Cardiac Risks of Operations to Improve Preoperative Cardiac Risk Assessment. Anesthesiology 2018;128:283-92.
46. Abelha FJ, Castro MA, Landeiro NM, Neves AM, Santos CC. Mortality and length of stay in a surgical intensive care unit. Rev Bras Anestesiol 2006;56(1):34-45.
47. Bertges DJ, Neal D, Schanzer A, et al. The Vascular Quality Initiative Cardiac Risk Index for prediction of myocardial infarction after vascular surgery. J Vasc Surg 2016;64:1411-21.
48. Bertges DJ, Goodney PP, Zhao Y, et al. The Vascular Study Group of New England Cardiac Risk Index (VSG-CRI) predicts cardiac complications more accurately than the Revised Cardiac Risk Index in vascular surgery patients. J Vasc Surg 2010;52:674-83.
49. Moodley Y, Naidoo P, Biccard BM. The South African Vascular Surgical Cardiac Risk Index (SAVS-CRI): a prospective observational study. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde 2013;103:746-50.
50. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney inter., Suppl. 2012; 2: 1–138.
51. Mehta RL, Kellum JA, Shah SV, *et al*. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Critical Care 2007;11(2):R31.
52. Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Critical Care 2004;8(4):R204-12.
53. Kheterpal S, Tremper KK, Heung M, et al. Development and validation of an acute kidney injury risk index for patients undergoing general surgery: results from a national data set. Anesthesiology 2009;110:505-15.
54. Moll FL, Powell JT, Fraedrich G, et al. Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. Eur J Vasc Endovasc Surg 2011;41 Suppl 1:S1-S58.
55. Saratzis AN, Goodyear S, Sur H, Saedon M, Imray C, Mahmood A. Acute kidney injury after endovascular repair of abdominal aortic aneurysm. Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists 2013;20:315-30.
56. Saratzis A, Melas N, Mahmood A, Sarafidis P. Incidence of Acute Kidney Injury (AKI) after Endovascular Abdominal Aortic Aneurysm Repair (EVAR) and Impact on Outcome. Eur J Vasc Endovasc Surg 2015;49:534-40.
57. Kellum JA, Lameire N. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Critical Care 2013;17:204.
58. Kashani K, Steuernagle JHt, Akhoundi A, Alsara A, Hanson AC, Kor DJ. Vascular Surgery Kidney Injury Predictive Score: A Historical Cohort Study. J Cardiothorac Vasc Anesth 2015;29:1588-95.
59. Johnson AP, Altmark RE, Weinstein MS, Pitt HA, Yeo CJ, Cowan SW. Predicting the Risk of Postoperative Respiratory Failure in Elective Abdominal and Vascular Operations Using the National Surgical Quality Improvement Program (NSQIP) Participant Use Data File. Ann Surg 2017;266:968-74.
60. Genovese EA, Fish L, Chaer RA, Makaroun MS, Baril DT. Risk stratification for the development of respiratory adverse events following vascular surgery using the Society of Vascular Surgery's Vascular Quality Initiative. J Vasc Surg 2017;65:459-70.

61. Antman E, Bassand J-P, Klein W, et al. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology committee for the redefinition of myocardial infarction. Journal of the American College of Cardiology 2000;36:959-69.
62. Collins GS, Reitsma JB, Altman DG, Moons KG, Group T. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. The TRIPOD Group. Circulation 2015;131:211-9.
63. Dover M, Tawfick W, Hynes N, Sultan S. Evaluation of illness severity scoring systems and risk prediction in vascular intensive care admissions. Vascular 2016;24:390-403.
64. Midwinter MJ, Tytherleigh M, Ashley S. Mortality and morbidity risk in Vascular Surgery using POSSUM and Portsmouth predictor equation. Br J Surg 1999;86:471-4
65. Sohail I, Jonker L, Stanton A, Walker M, Joseph T. Physiological POSSUM as an indicator for long-term survival in vascular surgery. Eur J Vasc Endovasc Surg 2013;46:223-6.
66. Teixeira IM, Teles AR, Castro JM, Azevedo LF, Mourao JB. Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity (POSSUM) System for Outcome Prediction in Elderly Patients Undergoing Major Vascular Surgery. J Cardiothorac Vasc Anesth 2018;32:960-7.
67. Maile MD, Jewell ES, Engoren MC. Timing of Preoperative Troponin Elevations and Postoperative Mortality After Noncardiac Surgery. Anesth Analg 2016;123:135-40.
68. Stather PW, Sidloff D, Dattani N, Choke E, Bown MJ, Sayers RD. Systematic review and meta-analysis of the early and late outcomes of open and endovascular repair of abdominal aortic aneurysm. Br J Surg 2013;100:863-72.
69. Thomas DM, Hulten EA, Ellis ST, et al. Open versus Endovascular Repair of Abdominal Aortic Aneurysm in the Elective and Emergent Setting in a Pooled Population of 37,781 Patients: A Systematic Review and Meta-Analysis. ISRN Cardiol 2014;2014:149243.
70. Sutzko DC, Andraska EA, Obi AT, Henke PK, Osborne NH. Risk Factors Associated with Perioperative Myocardial Infarction in Major Open Vascular Surgery. Ann Vasc Surg 2018;47:24-30.
71. Bakker EJ, Valentijn TM, Luijtgaarden KM, et al. Type 2 diabetes mellitus, independent of insulin use, is associated with an increased risk of cardiac complications after vascular surgery. Anaesth Intensive Care 2013;41:584-90.
72. Ford MK, Beattle WS, Wijeysundera DN. Systematic Review: Prediction of Perioperative Cardiac Complications and Mortality by the Revised Cardiac Risk Index. Ann Intern Med 2010;152:26-35.
73. Dover M, Tawfick W, Hynes N, Sultan S. Cardiac risk assessment, morbidity prediction, and outcome in the vascular intensive care unit. Vascular and endovascular surgery 2013;47:585-94.
74. Fronczek J, Polok K, Devereaux PJ, et al. External validation of the Revised Cardiac Risk Index and National Surgical Quality Improvement Program Myocardial Infarction and Cardiac Arrest calculator in noncardiac vascular surgery. Br J Anaesth 2019;123:421-9.
75. Gualandro DM, Puelacher C, LuratiBuse G, et al. Prediction of major cardiac events after vascular surgery. J Vasc Surg 2017;66:1826-35.
76. Gupta PK, Gupta H, Sundaram A, et al. Development and validation of a risk calculator for prediction of cardiac risk after surgery. Circulation 2011;124:381-7.
77. Parmar CD, Torella F. Prediction of major adverse cardiac events in vascular surgery: are cardiac risk scores of any practical value? Vascular and endovascular surgery 2010;44:14-9.
78. Diamond KR, Woo K, Neal D, et al. Prediction of postoperative myocardial infarction after suprainguinal bypass using the Vascular Quality Initiative Cardiac Risk Index. J Vasc Surg 2019;69:1831-9.
79. Minami K, Sugiyama Y, Iida H. A retrospective observational cohort study investigating the association between acute kidney injury and all-cause mortality among patients undergoing endovascular repair of abdominal aortic aneurysms. J Anesth 2017;31:686-91.

80. Zettervall SL, Ultee KHJ, Soden PA, et al. Predictors of renal dysfunction after endovascular and open repair of abdominal aortic aneurysms. J Vasc Surg 2017;65:991-6.
81. Duceppe E, Studzinska D, Devereaux PJ, et al. Incidence and predictors of myocardial and kidney injury following endovascular aortic repair: a retrospective cohort study. Canadian journal of anaesthesia = Journal canadien d'anesthesie 2019;66:1338-46.
82. Ruppert V, Leurs LJ, Steckmeier B, Buth J, Umscheid T. Influence of anesthesia type on outcome after endovascular aortic aneurysm repair: an analysis based on EUROSTAR data. J Vasc Surg 2006;44:16-21.
83. Chen SL, Kabutey NK, Whealon MD, Kuo IJ, Donayre CE, Fujitani RM. Locoregional Anesthesia Offers Improved Outcomes after Endovascular Repair of Ruptured Abdominal Aortic Aneurysms. Ann Vasc Surg 2019;59:134-42.
84. Harky A, Ahmad MU, Santoro G, Eriksen P, Chaplin G, Theologou T. Local Versus General Anesthesia in Nonemergency Endovascular Abdominal Aortic Aneurysm Repair: A Systematic Review and Meta-Analysis. J Cardiothorac Vasc Anesth 2019;1-9.
85. Faizer R, Weinhandl E, El Hag S, et al. Decreased mortality with local versus general anesthesia in endovascular aneurysm repair for ruptured abdominal aortic aneurysm in the Vascular Quality Initiative database. J Vasc Surg 2019;70:92-101.
86. Chalikias G, Drosos I, Tiakas DN. Contrast-induced Acute Kidney Injury: an update. Cardiovasc Drugs Ther 2016;30:215–28.
87. Mehran R, Dangas GD, Weisbord SD. Contrast-Associated Acute Kidney Injury. NEJM 2019;380:2146-55.
88. Chaykovska L, Heunisch F, von Einem G, et al. Urinary cGMP predicts major adverse renal events in patients with mild renal impairment and/or diabetes mellitus before exposure to contrast medium. PloS one 2018;13:e0195828.
89. Harris DG, Koo G, McCrone MP, et al. Acute Kidney Injury in Critically Ill Vascular Surgery Patients is Common and Associated with Increased Mortality. Front Surg 2015;2:8.
90. Hobson C, Lysak N, Huber M, Scali S, Bihorac A. Epidemiology, outcomes, and management of acute kidney injury in the vascular surgery patient. J Vasc Surg 2018;68:916-28.
91. van Waes JA, van Klei WA, Wijeysundera DN, van Wolfswinkel L, Lindsay TF, Beattie WS. Association between Intraoperative Hypotension and Myocardial Injury after Vascular Surgery. Anesthesiology 2016;124:35-44.
92. James MT, Pannu N. Can Acute Kidney Injury Be Considered a Clinical Quality Measure. Nephron 2015;131:237-41.
93. Abbott TEF, Fowler AJ, Pelosi P, et al. A systematic review and consensus definitions for standardised end-points in perioperative medicine: pulmonary complications. Br J Anaesth 2018;120:1066-79.
94. Chun TT, Garcia-Toca M, Eng JF, et al. Postoperative Infections are Associated with Increased Risk of Cardiac Events in Vascular Patients. Ann Vasc Surg 2017;41:151-9.
95. Neto AS, da Costa LGV, Hemmes SNT, et al. The LAS VEGAS risk score for prediction of postoperative pulmonary complications: An observational study. Eur J Anaesthesiol 2018;35:691-701.
96. Bauer SM, Cayne NS, Veith FJ. New developments in the preoperative evaluation and perioperative management of coronary artery disease in patients undergoing vascular surgery. J Vasc Surg 2010;51:242-51.
97. Siracuse JJ, Meltzer EC, Gill HL, et al. Outcomes and risk factors of cardiac arrest after vascular surgery procedures. J Vasc Surg 2015;61:197-202.
98. Juo YY, Mantha A, Ebrahimi R, Ziaeian B, Benharash P. Incidence of Myocardial Infarction After High-Risk Vascular Operations in Adults. JAMA surgery 2017;152:e173360.
99. Stojanovic MD, Markovic DZ, Vukovic AZ, et al. Enhanced Recovery after Vascular Surgery. Front Med (Lausanne) 2018;5:2.

100. Golubovic M, Peric V, Stanojevic D, et al. Potential New Approaches in Predicting Adverse Cardiac Events One Month after Major Vascular Surgery. Med Princ Pract 2019;28:63-9.
101. Roshanov PS, Walsh M, Devereaux PJ, et al. External validation of the Revised Cardiac Risk Index and update of its renal variable to predict 30-day risk of major cardiac complications after non-cardiac surgery: rationale and plan for analyses of the VISION study. BMJ Open 2017;7:e013510.
102. Otaki Y, Takahashi H, Watanabe T, et al. Cystatin C-based eGFR is a superior prognostic parameter to creatinine-based eGFR in post-endovascular therapy peripheral artery disease patients. Circ J 2015;79:2480-6.
103. Calvo-Vecino JM, Ripolles-Melchor J, Mythen MG, et al. Effect of goal-directed haemodynamic therapy on postoperative complications in low-moderate risk surgical patients: a multicentre randomised controlled trial (FEDORA trial). Br J Anaesth 2018;120:734-44.
104. Ranucci M, Johnson I, Willcox T, et al. Goal-directed perfusion to reduce acute kidney injury: A randomized trial. J Thorac Cardiovasc Surg 2018;156:1918-27.
105. Beitland S, Joannidis M. Biomarkers of acute kidney injury - a mission impossible? Acta Anaesthesiol Scand 2018;62:2-5.
106. Bolliger D, Siegemund M. The More, the Merrier? - Urinary Biomarkers for Prediction of Acute Kidney Injury After Cardiac Surgery. J Cardiothorac Vasc Anesth 2018;32:2201-2.
107. Nam K, Jeon Y, Kim WH, et al. Intraoperative glucose variability, but not average glucose concentration, may be a risk factor for acute kidney injury after cardiac surgery: a retrospective study. Canadian journal of anaesthesia = Journal canadien d'anesthesie 2019;66:921-33.
108. Vogel TR, Smith JB, Kruse RL. The association of postoperative glycemic control and lower extremity procedure outcomes. J Vasc Surg 2017;66:1123-32.
109. Mitchell SC, Vinnakota A, Deo SV, et al. Relationship between intraoperative serum lactate and hemoglobin levels on postoperative renal function in patients undergoing elective cardiac surgery. J Card Surg 2018;33:316-21.
110. Patelis N, Kouvelos GN, Koutsoumpelis A, Moris D, Matsagkas MI, Arnaoutoglou E. An update on predictive biomarkers for major adverse cardiovascular events in patients undergoing vascular surgery. Journal of clinical anesthesia 2016;33:105-16.
111. Biccard BM, Naidoo P, de Vasconcellos K. What is the best pre-operative risk stratification tool for major adverse cardiac events following elective vascular surgery? A prospective observational cohort study evaluating pre-operative myocardial ischaemia monitoring and biomarker analysis. Anaesthesia 2012;67:389-95.
112. Golubovic M, Stanojevic D, Lazarevic M, et al. A Risk Stratification Model for Cardiovascular Complications during the 3-Month Period after Major Elective Vascular Surgery. Biomed Res Int 2018;2018:4381527.
113. Jarai R, Mahla E, Perkmann T, et al. Usefulness of pre-operative copeptin concentrations to predict post-operative outcome after major vascular surgery. The American journal of cardiology 2011;108:1188-95.
114. Markovic D, Jevtovic-Stoimenov T, Cosic V, et al. Clinical Utility of Survivin (BIRC5), Novel Cardiac Biomarker, as a Prognostic Tool Compared to High-sensitivity C-reactive Protein, Heart-type Fatty Acid Binding Protein and Revised Lee Score in Elderly Patients Scheduled for Major Non-cardiac Surgery: A Prospective Pilot Study. J Med Biochem 2018;37:110-20.
115. Schrimpf C, Gillmann HJ, Sahlmann B, et al. Renal function interferes with copeptin in prediction of major adverse cardiac events in patients undergoing vascular surgery. PloS one 2015;10:e0123093.
116. Hua P, Liu J, Tao J, et al. Safety and efficacy of the perioperative administration of recombinant human brain natriuretic peptide (rhBNP): a systematic review and meta-analysis. Ther Clin Risk Manag 2018;14:313-21.

117. Alatassi A, Habbal M, Tamim H, Sadat M, Al Qasim E, Arabi YM. Association between troponin-I levels and outcome in critically ill patients admitted to non-cardiac intensive care unit with high prevalence of cardiovascular risk factors. BMC Anesthesiol 2018;18:54.
118. Reed GW, Horr S, Young L, et al. Associations Between Cardiac Troponin, Mechanism of Myocardial Injury, and Long-Term Mortality After Noncardiac Vascular Surgery. Journal of the American Heart Association 2017;6.
119. Gillmann HJ, Meinders A, Grohennig A, et al. Perioperative levels and changes of high-sensitivity troponin T are associated with cardiovascular events in vascular surgery patients. Critical care medicine 2014;42:1498-506.
120. Humble CAS, Huang S, Jammer I, Bjork J, Chew MS. Prognostic performance of preoperative cardiac troponin and perioperative changes in cardiac troponin for the prediction of major adverse cardiac events and mortality in noncardiac surgery: A systematic review and meta-analysis. PloS one 2019;14:e0215094.
121. Shen JT, Xu M, Wu Y, et al. Association of pre-operative troponin levels with major adverse cardiac events and mortality after noncardiac surgery: A systematic review and meta-analysis. Eur J Anaesthesiol 2018;35:815-24.
122. Zhao BC, Liu WF, Deng QW, et al. Meta-analysis of preoperative high-sensitivity cardiac troponin measurement in non-cardiac surgical patients at risk of cardiovascular complications. Br J Surg 2020;107:e81-e90.
123. Ali TZ, Lehman EB, Aziz F. Modified Frailty Index Can Be Used to Predict Adverse Outcomes and Mortality after Lower Extremity Bypass Surgery. Ann Vasc Surg 2018;46:168-77.
124. Ehlert BA, Najafian A, Orion KC, Malas MB, Black JH, 3rd, Abularrage CJ. Validation of a modified Frailty Index to predict mortality in vascular surgery patients. J Vasc Surg 2016;63:1595-601.
125. Eslami MH, Saadeddin Z, Rybin DV, Doros G, Siracuse JJ, Farber A. Association of frailty index with perioperative mortality and in-hospital morbidity after elective lower extremity bypass. J Vasc Surg 2019;69:863-74.
126. Fang ZB, Hu FY, Arya S, Gillespie TW, Rajani RR. Preoperative frailty is predictive of complications after major lower extremity amputation. J Vasc Surg 2017;65:804-11.
127. Hall DE, Arya S, Schmid KK, et al. Association of a Frailty Screening Initiative With Postoperative Survival at 30, 180, and 365 Days. JAMA surgery 2017;152:233-40.
128. Karam J, Tsiouris A, Shepard A, Velanovich V, Rubinfeld I. Simplified frailty index to predict adverse outcomes and mortality in vascular surgery patients. Ann Vasc Surg 2013;27:904-8.
129. McIsaac DI, Bryson GL, van Walraven C. Association of Frailty and 1-Year Postoperative Mortality Following Major Elective Noncardiac Surgery: A Population-Based Cohort Study. JAMA surgery 2016;151:538-45.
130. O'Neill BR, Batterham AM, Hollingsworth AC, Durrand JW, Danjoux GR. Do first impressions count? Frailty judged by initial clinical impression predicts medium-term mortality in vascular surgical patients. Anaesthesia 2016;71:684-91.
131. Partridge JS, Fuller M, Harari D, Taylor PR, Martin FC, Dhesi JK. Frailty and poor functional status are common in arterial vascular surgical patients and affect postoperative outcomes. International journal of surgery 2015;18:57-63.
132. Rothenberg KA, George EL, Trickey AW, et al. Assessment of Risk Analysis Index for Prediction of Mortality, Major Complications and Length of Stay in Vascular Surgery Patients. Ann Vasc Surg 2020.

10. References from published papers (alphabetic order)

1. Abelha FJ, Castro MA, Landeiro NM, Neves AM, Santos CC. Mortality and length of stay in a surgical intensive care unit. Rev Bras Anestesiol 2006;56(1):34-45.
2. Abelha FJ, Botelho M, Fernandes V, Barros H. Quality of life and mortality assessment in patients with major cardiac events in the postoperative period. Rev Bras Anestesiol 2010;60(3):268-84.
3. Ad N, Holmes SD, Massimiano PS, et al. Operative risk and preoperative hematocrit in bypass graft surgery: Role of gender and blood transfusion. Cardiovascular Revascularization Medicine 2015;16(7):397-400.
4. Agha RA, Borrelli MR, Vella-Baldacchino M, Thavayogan R and Orgill DP, for the STROCSS Group. The STROCSS Statement: Strengthening the Reporting of Cohort Studies in Surgery. International Journal of Surgery 2017;46:198-202.
5. Anghel D, Anghel R, Corciova F, Enache M, Tinica G. Preoperative arrhythmias such as atrial fibrillation: cardiovascular surgery risk factor. Biomed Res Int 2014(2014):584918.
6. Antman E, Bassand J-P, Klein W, et al. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology committee for the redefinition of myocardial infarction. J Am Coll Cardiol 2000;36:959-69.
7. Arora P, Davari-Farid S, Pourafkari L et al. The effect of acute kidney injury after revascularization on the development of chronic kidney disease and mortality in patients with chronic limb ischemia. J Vasc Surg 2015;61(3):720-7.
8. Bakker EJ, Valentijn TM, Luijtgaarden KM, et al. Type 2 diabetes mellitus, independent of insulin use, is associated with an increased risk of cardiac complications after vascular surgery. Anaesth Intensive Care 2013;41:584-90.
9. Bertges DJ, Goodney PP, Zhao Y, et al. The Vascular Study Group of New England Cardiac Risk Index (VSG-CRI) predicts cardiac complications more accurately than the Revised Cardiac Risk Index in vascular surgery patients. J Vasc Surg 2010;52:674-83.
10. Bertges DJ, Neal D, Schanzer A, et al. The Vascular Quality Initiative Cardiac Risk Index for prediction of myocardial infarction after vascular surgery. J Vasc Surg 2016;64:1411-21.
11. Biccard BM, Scott DJA, Chan MTV, et al. Myocardial Injury After Noncardiac Surgery (MINS) in Vascular Surgical Patients: A Prospective Observational Cohort Study. Ann Surg 2018;268(2):357-63.
12. Biccard BM. Detection and management of perioperative myocardial ischemia. Current Opinion in Anaesthesiology 2014;27:336-43.
13. Bilimoria KY, Liu Y, Paruch JL, et al. Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons. Journal of the American College of Surgeons 2013;217(5):833-42.
14. Chen SL, Whealon MD, Kabutey NK, Kuo IJ, Sgroi MD, Fujitani RM. Outcomes of open and endovascular lower extremity revascularization in active smokers with advanced peripheral arterial disease. J Vasc Surg 2017;65(6):1680-9.
15. Darmon M, Diconne E, Souweine B, Ruckly S, Adrie C, Azoulay E, et al. Prognostic consequences of borderline dysnatremia: pay attention to minimal serum sodium change. Critical Care 2013;17(1):R12.
16. Darmon M, Timsit JF, Francais A, et al. Association between hypernatraemia acquired in the ICU and mortality: a cohort study. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association 2010;25(8):2510-5.
17. Devereaux PJ, Chan MT, Alonso-Coello P, Walsh M, Berwanger O, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. JAMA 2012;307(21):2295-304.
18. Egorova N, Giacovelli JK, Gelijns A, et al. Defining high-risk patients for endovascular aneurysm repair. J Vasc Surg 2009;50:1271-9.

19. Elisha S, Nagelhout J, Heiner J, Gabot M. Anesthesia case management for endovascular aortic aneurysm repair. AANA J 2014;82(2):145-52.
20. Flores E, Lewinger JP, Rowe VL, Woo K, Weaver FA, Shavelle D, et al. Increased risk of mortality after lower extremity bypass in individuals with acute kidney injury in the Vascular Quality Initiative. J Vasc Surg 2017;65(4):1055-61.
21. Ford MK, Beattle WS, Wijeysundera DN. Systematic Review: Prediction of Perioperative Cardiac Complications and Mortality by the Revised Cardiac Risk Index. Ann Intern Med 2010;152:26-35.
22. Franz R, Hartman J, Wright M. Comparison of anesthesia technique on outcomes of endovascular repair of abdominal aortic aneurysms: a five-year review of monitored anesthesia care with local anesthesia vs. general or regional anesthesia. J Cardiovasc Surg (Torino) 2011;52(4):567-77.
23. Funk GC, Lindner G, Druml W, et al. Incidence and prognosis of dysnatremias present on ICU admission. Intensive Care Medicine. 2010;36(2):304-11.
24. Ghaferi AA, Birkmeyer JD, Dimick JB. Variation in hospital mortality associated with inpatient surgery. NEJM 2009;361(14):1368-75.
25. Gillmann HJ, Meinders A, Grohennig A, et al. Perioperative levels and changes of high-sensitivity troponin T are associated with cardiovascular events in vascular surgery patients. Critical Care Medicine 2014;42:1498-506.
26. Gupta PK, Gupta H, Sundaram A, et al. Development and validation of a risk calculator for prediction of cardiac risk after surgery. Circulation 2011;124:381-7.
27. Gupta PK, Sundaram A, MacTaggart JN, et al. Preoperative anemia is an independent predictor of postoperative mortality and adverse cardiac events in elderly patients undergoing elective vascular operations. Ann Surg 2013;258(6):1096-102.
28. Hall BL, Hamilton BH, Richards K, Bilimoria KY, Cohen ME, Ko CY. Does surgical quality improve in the American College of Surgeons National Surgical Quality Improvement Program: an evaluation of all participating hospitals. Ann Surg 2009;250(3):363-76.
29. Halpern NA, Pastores SM, Greenstein RJ. Critical care medicine in the United States 1985-2000: analysis of bed numbers, use, and costs. Critical Care Medicine 2004;32(6):1254-9.
30. Hendriks EJ, Westerink J, de Jong PA, et al. Association of High Ankle Brachial Index With Incident Cardiovascular Disease and Mortality in a High-Risk Population. Arterioscler Thromb Vasc Biol 2016;36(2):412-17.
31. Huber M, Ozrazgat-Baslanti T, Thottakkara P, et al. Mortality and Cost of Acute and Chronic Kidney Disease after Vascular Surgery. Ann Vasc Surg 2016;30:72-81.
32. Huber M, Ozrazgat-Baslanti T, Thottakkara P, Scali S, Bihorac A, Hobson C. Cardiovascular-Specific Mortality and Kidney Disease in Patients Undergoing Vascular Surgery. JAMA Surg 2016;151(5):441-50.
33. Jammer I, Wickboldt N, Sander M, et al. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: a statement from the ESA-ESICM joint taskforce on perioperative outcome measures. Eur J Anaesthesiol 2015;32(2):88-105.
34. Jarai R, Mahla E, Perkmann T, et al. Usefulness of pre-operative copeptin concentrations to predict post-operative outcome after major vascular surgery. American Journal of Cardiology 2011;108:1188-95.
35. Kashani K, Steuernagle JHt, Akhoundi A, Alsara A, Hanson AC, Kor DJ. Vascular Surgery Kidney Injury Predictive Score: A Historical Cohort Study. J Cardiothorac Vasc Anesth 2015;29(6):1588-95.
36. Khuri SF, Henderson WG, DePalma RG, et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Ann Surg 2005;242:326-41.
37. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Critical Care Medicine. 1985;13(10):818-29.

38. Kristensen SD, Knuuti J, Saraste A, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). Eur J Anaesthesiol 2014;31(10):517-73.
39. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993;270(24):2957-63.
40. Le Manach Y, Collins G, Rodseth R, et al. Preoperative Score to Predict Postoperative Mortality (POSPOM): Derivation and Validation. Anesthesiology 2016;124(3):570-9.
41. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and Prospective Validation of a Simple Index for Prediction of Cardiac Risk of Major Noncardiac Surgery. Circulation 1999;100:1043-9.
42. Leung JM, Dzankic S. Relative importance of preoperative health status versus intraoperative factors in predicting postoperative adverse outcomes in geriatric surgical patients. Journal of the American Geriatrics Society 2001;49(8):1080-5.
43. Liem VGB, Hoeks SE, Grune F, et al. Prognostic value of postoperative high-sensitivity troponin T in patients with different stages of kidney disease undergoing noncardiac surgery. Br J Anaesth 2018;120:84-93.
44. Lindner G, Funk GC. Hypernatremia in critically ill patients. Journal of Critical Care 2013;28(2):216 e11-20.
45. Liu JB, Liu Y, Cohen ME, Ko CY, Sweitzer BJ. Defining the Intrinsic Cardiac Risks of Operations to Improve Preoperative Cardiac Risk Assessment. Anesthesiology 2018;128:283-92.
46. Liu Y, Cohen ME, Ko CY, Bilimoria KY, Hall BL. Considerations in Releasing Equations for the American College of Surgeons NSQIP Surgical Risk Calculator: In Reply to Wanderer and Ehrenfeld. Journal of the American College of Surgeons 2016;223(4):674-5.
47. Lobo SM, Rezende E, Knibel MF, Silva NB, Paramo JA, Nacul FE, et al. Early determinants of death due to multiple organ failure after noncardiac surgery in high-risk patients. Anesth Analg 2011;112(4):877-83.
48. Lorentz MN, Boni CL, Soares RR. Anesthesia for endovascular surgery of the abdominal aorta. Rev Bras Anestesiol 2008;58(5):525-32.
49. Maia PC, Abelha FJ. Predictors of major postoperative cardiac complications in a surgical ICU. Revista portuguesa de cardiologia : orgao oficial da Sociedade Portuguesa de Cardiologia = Portuguese journal of cardiology : an official journal of the Portuguese Society of Cardiology 2008;27(3):321-8.
50. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Critical Care 2007;11(2):R31.
51. Midwinter MJ, Tytherleigh M, Ashley S. Mortality and morbidity risk in Vascular Surgery using POSSUM and Portsmouth predictor equation. Br J Surg 1999;86:471-4.
52. Mills JL, Sr., Duong ST, Leon LR, Jr., et al. Comparison of the effects of open and endovascular aortic aneurysm repair on long-term renal function using chronic kidney disease staging based on glomerular filtration rate. J Vasc Surg 2008;47(6):1141-9.
53. Mohammedi K, Potier L, Belhatem N, Matallah N, Hadjadj S, Roussel R, et al. Lower-extremity amputation as a marker for renal and cardiovascular events and mortality in patients with long standing type 1 diabetes. Cardiovascular Diabetology 2016;15:5.
54. Moll FL, Powell JT, Fraedrich G, et al. Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. Eur J Vasc Endovasc Surg 2011;41 Suppl 1:S1-S58.
55. Monk TG, Saini V, Weldon BC, Sigl JC. Anesthetic management and one-year mortality after noncardiac surgery. Anesth Analg 2005;100(1):4-10.
56. Monseu M, Gand E, Saulnier PJ, et al. Acute Kidney Injury Predicts Major Adverse Outcomes in Diabetes: Synergic Impact With Low Glomerular Filtration Rate and Albuminuria. Diabetes Care 2015;38(12):2333-40.

57. Moodley Y, Naidoo P, Biccard BM. The South African Vascular Surgical Cardiac Risk Index (SAVS-CRI): a prospective observational study. South African Medical Journal = Suid-Afrikaanse tydskrif vir geneeskunde 2013;103:746-50.
58. Mosquera D, Chiang N, Gibberd R. Evaluation of surgical performance using V-POSSUM risk-adjusted mortality rates. ANZ Journal of Surgery 2008;78(7):535-9.
59. Naughton C, Feneck RO. The impact of age on 6-month survival in patients with cardiovascular risk factors undergoing elective non-cardiac surgery. International Journal of Clinical Practice 2007;61(5):768-76.
60. O'Hare AM, Sidawy AN, Feinglass J, et al. Influence of renal insufficiency on limb loss and mortality after lower extremity surgical revascularization. J Vasc Surg 2004;39(4):709-16.
61. Ohlsson H, Winso O. Assessment of the Surgical Apgar Score in a Swedish setting. Acta Anaesthesiologica Scandinavica. 2011;55(5):524-9.
62. O'Keeffe SD, Davenport DL, Minion DJ, Sorial EE, Endean ED, Xenos ES. Blood transfusion is associated with increased morbidity and mortality after lower extremity revascularization. J Vasc Surg 2010;51(3):616-21.
63. Ollila A, Vikatmaa L, Virolainen J, et al. Perioperative Myocardial Infarction in Non-Cardiac Surgery Patients: A Prospective Observational Study. Scandinavian journal of surgery : SJS : official organ for the Finnish Surgical Society and the Scandinavian Surgical Society 2017;106:180-6.
64. O'Neal WT, Efird JT, Davies SW, Choi YM, Anderson CA, Kindell LC, et al. Preoperative atrial fibrillation and long-term survival after open heart surgery in a rural tertiary heart institute. Heart & lung : the Journal of Critical Care 2013;42(6):442-7.
65. Opprea AD, Lombard FW, Liu WW, et al. Baseline Pulse Pressure, Acute Kidney Injury, and Mortality After Noncardiac Surgery. Anesth Analg 2016;123(6):1480-9.
66. Paravastu SC, Jayarajasingam R, Cottam R, Palfreyman SJ, Michaels JA, Thomas SM. Endovascular repair of abdominal aortic aneurysm. Cochrane Database Syst Rev. 2014 Jan 23;(1):CD004178. doi: 10.1002/14651858.
67. Parmar CD, Torella F. Prediction of major adverse cardiac events in vascular surgery: are cardiac risk scores of any practical value? Vascular and Endovascular Surgery 2010;44:14-9.
68. Patelis N, Kouvelos GN, Koutsoumpelis A, Moris D, Matsagkas MI, Arnaoutoglou E. An update on predictive biomarkers for major adverse cardiovascular events in patients undergoing vascular surgery. Journal of Clinical Anesthesia 2016;33:105-16.
69. Pearse RM, Harrison DA, James P, et al. Identification and characterization of the high-risk surgical population in the United Kingdom. Critical Care 2006;10(3):R81.
70. Pearse RM, Moreno RP, Bauer P, et al. Mortality after surgery in Europe: a 7 day cohort study. Lancet. 2012;380(9847):1059-65.
71. Puelacher C, Lurati Buse G, Seeberger D, et al. Perioperative Myocardial Injury After Noncardiac Surgery: Incidence, Mortality, and Characterization. Circulation 2018;137(12):1221-32.
72. Reed GW, Horr S, Young L, et al. Associations Between Cardiac Troponin, Mechanism of Myocardial Injury, and Long-Term Mortality After Noncardiac Vascular Surgery. Journal of the American Heart Association 2017;6:e005672.
73. Rhodes A, Moreno RP, Metnitz B, Hochrieser H, Bauer P, Metnitz P. Epidemiology and outcome following post-surgical admission to critical care. Intensive Care Medicine 2011;37(9):1466-72.
74. Rochanov PS, Walsh M, Deveraux PJ, et al. External validation of the Revised Cardiac Risk Index and update of its renal variable to predict 30-day risk of major cardiac complications after non-cardiac surgery: rationale and plan for analyses of the VISION study. BMJ Open 2017;7:e013510.
75. Ruppert V, Leurs LJ, Steckmeier B, Buth J, Umscheid T. Influence of anesthesia type on outcome after endovascular aortic aneurysm repair: an analysis based on EUROSTAR data. J Vasc Surg 2006;44(1):16-21.

76. Sailer AM, Nelemans PJ, van Berlo C, Yazar O, de Haan MW, Fleischmann D, et al. Endovascular treatment of complex aortic aneurysms: prevalence of acute kidney injury and effect on long-term renal function. Eur Radiol 2016;26(6):1613-9.
77. Saratzis A, Melas N, Mahmood A, Sarafidis P. Incidence of Acute Kidney Injury (AKI) after Endovascular Abdominal Aortic Aneurysm Repair (EVAR) and Impact on Outcome. Eur J Vasc Endovasc Surg 2015;49(5):534-40.
78. Saratzis AN, Goodyear S, Sur H, Saedon M, Imray C, Mahmood A. Acute kidney injury after endovascular repair of abdominal aortic aneurysm. J Endovasc Ther 2013;20(3):315-30.
79. Scali S, Bertges D, Neal D, et al. Heart rate variables in the Vascular Quality Initiative are not reliable predictors of adverse cardiac outcomes or mortality after major elective vascular surgery. J Vasc Surg 2015;62:710-20.
80. Schrimpf C, Gillmann HJ, Sahlmann B, et al. Renal function interferes with copeptin in prediction of major adverse cardiac events in patients undergoing vascular surgery. PloS One 2015;10:e0123093.
81. Sessler DI, Devereaux PJ. Perioperative Troponin Screening. Anesth Analg 2016;123:359-60.
82. Simpson JC, Moonesinghe SR. Introduction to the postanaesthetic care unit. Perioperative Medicine 2013;2(1):5.
83. Singh TP, Morris DR, Smith S, Moxon JV, Golledge J. Systematic Review and Meta-Analysis of the Association Between C-Reactive Protein and Major Cardiovascular Events in Patients with Peripheral Artery Disease. Eur J Vasc Endovasc Surg 2017;54:220-33.
84. Skonetzki S, Lüders F, Engelbertz C, Malyar NM, Freisinger E, Meyborg M et al. Aging and Outcome in Patients With Peripheral Artery Disease and Critical Limb Ischemia. Journal of Post-Acute and Long-Term Care Medicine 2016;17(10):927-32.
85. Smaka TJ, Cobas M, Velazquez OC, Lubarsky DA. Perioperative management of endovascular abdominal aortic aneurysm repair: update 2010. J Cardiothorac Vasc Anesth 2011;25(1):166-76.
86. Smeili LA, Lotufo PA. Incidence and Predictors of Cardiovascular Complications and Death after Vascular Surgery. Arquivos Brasileiros de Cardiologia 2015;105:510-8.
87. Stather PW, Sidloff D, Dattani N, Choke E, Bown MJ, Sayers RD. Systematic review and meta-analysis of the early and late outcomes of open and endovascular repair of abdominal aortic aneurysm. Br J Surg 2013;100(7):863-72.
88. Stelfox HT, Ahmed SB, Khandwala F, Zygun D, Shahpori R, Laupland K. The epidemiology of intensive care unit-acquired hyponatraemia and hypernatraemia in medical-surgical intensive care units. Critical Care 2008;12(6):R162.
89. Thomas DM, Hulten EA, Ellis ST, Anderson DM, Anderson N, McRae F, et al. Open versus Endovascular Repair of Abdominal Aortic Aneurysm in the Elective and Emergent Setting in a Pooled Population of 37,781 Patients: A Systematic Review and Meta-Analysis. ISRN Cardiol 2014:149243.
90. Thomas KN, Cotter JD, Williams MJ, van Rij AM. Diagnosis, Incidence, and Clinical Implications of Perioperative Myocardial Injury in Vascular Surgery. Vascular and Endovascular Surgery 2016;50:247-55.
91. Valentijn TM, Hoeks SE, Bakker EJ, et al. The impact of perioperative red blood cell transfusions on postoperative outcomes in vascular surgery patients. Ann Vasc Surg 2015;29(3):511-9.
92. van Lier F, Wesdorp F, Liem VGB, et al. Association between postoperative mean arterial blood pressure and myocardial injury after noncardiac surgery. Br J Anaest 2018;120:77-83.
93. Vanniyasingam T, Rodseth RN, Lurati Buse GA, et al. Predicting the occurrence of major adverse cardiac events within 30 days of a vascular surgery: an empirical comparison of the minimum p value method and ROC curve approach using individual patient data meta-analysis. SpringerPlus 2016;5:304.

94. Velescu A, Clará A, Cladellas M, et al. Anemia Increases Mortality After Open or Endovascular Treatment in Patients with Critical Limb Ischemia: A Retrospective Analysis. Eur J Vasc Endovasc Surg 2016;51(4):543-9.
95. Vincent JL, Moreno R. Clinical review: scoring systems in the critically ill. Critical Care 2010;14(2):207.
96. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453-7.
97. Waite MD, Fuhrman SA, Badawi O, Zuckerman IH, Franey CS. Intensive care unit-acquired hypernatremia is an independent predictor of increased mortality and length of stay. Journal of Critical Care 2013;28(4):405-12.
98. Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. Lancet 2008;372(9633):139-44.
99. Weissman C, Klein N. The importance of differentiating between elective and emergency postoperative critical care patients. Journal of Critical Care 2008;23(3):308-16.
100. Weissman C. The enhanced postoperative care system. Journal of Clinical Anesthesia 2005;17(4):314-22.
101. Welten GM, Schouten O, van Domburg RT, et al. The influence of aging on the prognostic value of the revised cardiac risk index for postoperative cardiac complications in vascular surgery patients. Eur J Vasc Endovasc Surg 2007;34:632-8.
102. Wylie SJ, Wong GT, Chan YC, Irwin MG. Endovascular aneurysm repair: a perioperative perspective. Acta Anaesthesiol Scand 2012;56(8):941-9.
103. Xie JX, Glorioso TJ, Dattilo PB, et al. Effect of Chronic Kidney Disease on Mortality in Patients Who Underwent Lower Extremity Peripheral Vascular Intervention. Am J Cardiol 2017;119:669-74

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