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**Impacto da fragilidade e da anemia pré-
operatória na recuperação de pacientes
submetidos à cirurgia de
revascularização do miocárdio**

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Dissertação submetida ao Programa de Pós-Graduação em Ciências da Reabilitação da Universidade Federal de Ciências da Saúde de Porto Alegre como requisito para a obtenção do grau de Mestre.

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**Impacto da fragilidade e da anemia pré-operatória na recuperação
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miocárdio**

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RESUMO

Introdução: embora a cirurgia de revascularização do miocárdio (CRM) seja o procedimento cardiovascular mais realizado em todo o mundo há décadas e tratamento padrão para doença arterial coronariana complexa, a predição do risco cirúrgico para o procedimento apresenta falhas importantes. Nesse contexto, a fragilidade e a anemia pré-operatória, fatores de risco ainda pouco estudados, podem ter um papel relevante na predição do risco cirúrgico. **Objetivos:** nosso objetivo foi avaliar o impacto da fragilidade e da anemia pré-operatória sobre os desfechos hospitalares pós-CRM. **Métodos:** nós montamos uma coorte de pacientes submetidos consecutivamente à CRM isolada entre janeiro de 2013 e dezembro de 2017. A fragilidade foi definida como qualquer deficiência no Índice de Katz. Dos 1508 pacientes, 126 (8,4%) foram classificados como frágeis. As características basais e os desfechos foram comparados por análise univariada. Modelos de regressão multivariada foram aplicados para análise ajustada dos desfechos de interesse. A acurácia preditiva dos modelos de regressão foi analisada por meio de curvas ROC. A acurácia preditiva adicional da fragilidade e da anemia, quando associadas com os escores de risco cirúrgico, foi apurada pela comparação das curvas ROC com o teste DeLong. **Resultados:** nós observamos que os pacientes frágeis apresentavam idade mais avançada, mais comorbidades associadas e a maioria era do sexo feminino. Nós verificamos também que a fragilidade foi um preditor independente para mortalidade hospitalar e para eventos cardiovasculares e cerebrovasculares graves - MACCE. Além disso, por meio de análise ajustada, nós identificamos que a fragilidade esteve associada com maior tempo de internação pós-procedimento. A anemia pré-operatória, da mesma forma que a fragilidade, foi classificada como um preditor independente para mortalidade hospitalar e para MACCE. No entanto, nós não encontramos associação significativa entre anemia e maior tempo de internação hospitalar. Adicionalmente, nós verificamos que quando associadas com os escores de risco cirúrgico, a fragilidade e a anemia melhoraram a acurácia preditiva do EuroScore 1 e do EuroScore 2 para mortalidade hospitalar. **Conclusões:** nós constatamos que a fragilidade e a anemia pré-operatória são preditores independentes de mortalidade hospitalar e de MACCE pós-CRM. A

fragilidade também foi um forte preditor de maior tempo de internação hospitalar. A associação da fragilidade e da anemia com os escores de risco cirúrgico resultou em uma melhora significativa da acurácia preditiva dos escores em relação à mortalidade hospitalar. A triagem da fragilidade pelo índice de Katz melhorou a avaliação de risco para CRM isolada e, quando associada à anemia, demonstrou que pacientes frágeis e anêmicos possuem piores resultados cirúrgicos. Identificar estes pacientes pode ainda resultar em cuidados pré-operatórios específicos para o manejo da fragilidade e da anemia pré-operatória.

Palavras-chave: fragilidade, anemia, revascularização do miocárdio, EuroScore, mortalidade, MACCE, tempo de internação

ABSTRACT

Background: Although CABG is the most commonly performed cardiovascular surgery in the world for decades, being the standard treatment for complex coronary artery disease, the prediction of surgical risk for the procedure still have important gaps. In this context, frailty and preoperative anemia, may have an unknown role in the prediction of surgical risk. **Objectives:** to evaluate the impact of fragility and preoperative anemia on hospital outcomes after CABG. **Methods:** We assembled a cohort of patients submitted consecutively to isolated CABG between January 2013 and December 2017. Frailty was defined as any impairment in the Katz Index. Of the 1508 patients, 126 (8.4%) were classified as frail. Baseline characteristics and outcomes were compared by univariate analysis. Multivariate regression models were applied for the adjusted analysis of the outcomes. The predictive accuracy of the regression models was analyzed by ROC curves. The additional predictive accuracy of the frailty and the anemia, when associated with the surgical risk scores, was analyzed by comparing the ROC curves with the DeLong test. **Results:** We found that the frail patients were older, more likely to be female, and had more associated comorbidities. We also found that frailty was an independent predictor for hospital mortality and for severe cardiovascular and cerebrovascular events - MACCE. In addition, we identified by adjusted analysis that frailty was associated with a longer period of hospitalization after the procedure. Preoperative anemia also was classified as an independent predictor for in-hospital mortality and MACCE. However, we found no significant association between anemia and longer hospital stay. Additionally, we were able to verify that when associated with surgical risk scores, frailty and anemia improved the predictive accuracy of EuroScore 1 and EuroScore 2 for in-hospital mortality. **Conclusions:** We verified that preoperative frailty and anemia are independent predictors of hospital mortality and MACCE after CABG. Frailty was also a strong predictor of longer hospital stay. The association of frailty and anemia with surgical risk scores resulted in a significant improvement in the predictive accuracy of the scores for hospital mortality. Frailty screening, performed by the Katz Index, improved the risk assessment for isolated CABG and, when associated with anemia, showed that fragile and anemic patients had worse

surgical outcomes. Identifying these patients may also result in specific preoperative care for the management of frailty and preoperative anemia.

Key words: fragility, anemia, myocardial revascularization, EuroScore, mortality, MACCE, length of hospital stay

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1 INTRODUÇÃO

A doença arterial coronariana possui prevalência elevada em todo o mundo. Por suas altas taxas de mortalidade e de morbidades, a prevenção e o tratamento das cardiopatias representam um setor fundamental e estratégico nos sistemas de saúde (1, 2).

Desde que foi estabelecida, em 1964, a cirurgia de revascularização do miocárdio (CRM) é o tratamento padrão para coronariopatias complexas. É, desde então, a cirurgia cardíaca mais realizada no mundo. No Brasil, o número de intervenções anuais é superior a 30 mil (3).

A associação de complicações cirúrgicas importantes com o uso da circulação extracorpórea (CEC) levou ao desenvolvimento da CRM sem CEC, uma alternativa menos invasiva e com resposta inflamatória menos intensa no organismo (4, 5). No entanto, o consenso atual é de que as duas técnicas possuem resultados similares em curto, médio e longo prazo (5-8).

Com os resultados ainda controversos relacionados às duas técnicas cirúrgicas, o estudo dos fatores de risco pré-operatórios tornou-se indispensável para uma avaliação acurada dos pacientes. Alguns destes fatores constituem os escores de risco cirúrgico consagrados na prática cardiológica, mas que, apesar da larga utilização, apresentam limitações importantes, capazes de subestimar ou superestimar o risco de acordo com a população estudada (9, 10).

O estudo prognóstico, portanto, ainda representa um grande desafio ao esbarrar na limitação dos escores de risco tradicionais. A necessidade de complementar e aprofundar a análise aumentou o interesse por modelos de avaliação adotados em outras áreas, como é o caso da fragilidade e da anemia (10, 11).

Apesar do grande potencial, sua aplicação também encontra barreiras: a avaliação da fragilidade não é padronizada e pode se tornar complexa pelo número de variáveis necessárias para classificar um paciente de acordo com a ferramenta utilizada (12). Como consequência, a busca por uma característica que isoladamente possa indicar com segurança se um paciente é frágil passou a ser alvo de estudos na área cardiovascular. Neste sentido, trabalhos recentes apresentaram

resultados promissores sobre o grau de mobilidade dos pacientes e os desfechos pós-operatórios (13).

Uma das ferramentas disponíveis para avaliar a mobilidade e capacidade funcional de um paciente é o Índice de Katz, que ganhou destaque em estudos prognósticos de intervenções cardíacas valvulares – investigações relacionaram classificações mais baixas do Índice de Katz a piores desfechos pós-implante valvular aórtico transcater (14).

Isso porque o índice desenvolvido por Katz e colaboradores em 1976 possibilita uma classificação simples e rápida da mobilidade dos pacientes com base na avaliação de seis parâmetros relacionados a atividades cotidianas básicas (12, 14). Apesar da aplicabilidade demonstrada pelo método e do incremento que representam na avaliação de risco, a utilização do Índice de Katz em pacientes encaminhados para cirurgia cardíaca ainda é baixa (14).

A anemia pré-operatória é outro fator de risco cardiovascular conhecido e está associada à capacidade funcional dos pacientes. Além de ter prevalência elevada em cardiopatas, afeta de forma significativa os resultados da CRM (15). Por ser uma condição debilitante e causar redução da massa muscular, é possível que a anemia tenha impacto no grau de mobilidade do paciente e, conseqüentemente, no Índice de Katz (16, 17).

Tendo em vista o cenário descrito até aqui e a necessidade de uma avaliação mais acurada dos pacientes submetidos ao procedimento cirúrgico cardiovascular mais realizado em todo o mundo – com estimativa de crescimento para os próximos anos devido especialmente ao aumento da expectativa de vida –, o objetivo deste trabalho foi verificar, por meio do Índice de Katz, se os pacientes com algum grau de comprometimento em suas atividades cotidianas básicas apresentam piores desfechos após serem submetidos à cirurgia de revascularização do miocárdio isolada e, ainda, se tais resultados são impactados pela ocorrência de anemia pré-operatória.

2. EMBASAMENTO TEÓRICO – CONTEXTUALIZAÇÃO

2. 1 Cirurgia de revascularização do miocárdio

Todos os anos, 16 milhões de mortes acontecem no mundo em decorrência de agravos relacionados ao sistema cardiovascular. Somente no Brasil, estimativas indicam que entre 1990 e 2020 as cardiopatias isquêmicas acumularão um crescimento de 130%. Tendo em vista a alta prevalência de doenças isquêmicas em nosso país, a elevada taxa de mortalidade e a condição debilitante que impõem aos pacientes acometidos, a prevenção e o tratamento das cardiopatias representam um setor fundamental e estratégico dentro do sistema de saúde (1).

A doença aterosclerótica coronariana, caracterizada pelo acúmulo de gordura no interior das artérias coronárias, é a patologia cardíaca mais comum. Estabelecido em 1964, o tratamento padrão para doenças coronarianas complexas é a cirurgia de revascularização do miocárdio (CRM). Por esta razão, é o procedimento cardíaco mais realizado em todo o mundo. No Brasil, o número de intervenções anuais é superior a 25 mil (3).

No procedimento cirúrgico de revascularização do miocárdio, enxertos venosos e arteriais são retirados dos membros inferiores e superiores e utilizados como dutos que ligam diretamente a porção inicial da artéria aorta com regiões distais às lesões coronarianas. A cirurgia pode ser realizada de forma isolada ou associada a outro procedimento cardíaco e, na maioria dos casos, não é dependente do suporte da circulação extracorpórea. Pode, portanto, ser realizada com o coração em atividade (18, 19).

Ao mesmo tempo em que a CRM com circulação extracorpórea (CEC) prolonga a vida e minimiza sintomas – quando comparada ao tratamento clínico e também ao tratamento percutâneo –, existem riscos significativos associados ao procedimento, inclusive de morte e de outras intercorrências graves (4, 5, 20). Na abordagem com CEC, as taxas de mortalidade perioperatória costumam ficar em torno de 2%, mas podem chegar a 9% dependendo das comorbidades associadas (5, 7).

A revascularização cirúrgica convencional é frequentemente associada com disfunção renal, intestinal e pulmonar. As complicações pulmonares pós-cirurgia cardíaca costumam ser correlacionadas, principalmente, com o manejo anestésico e incluem atelectasias, derrame pleural, insuficiência respiratória e pneumonia (21, 22). A atelectasia é o desfecho pulmonar mais comum e, além de estar associada com as manobras anestésicas, a disfunção diafragmática e a dor torácica exercem papéis importantes no desenvolvimento da complicação (22).

Complementarmente, a disfunção dos músculos respiratórios, decorrente da cirurgia cardíaca, resulta na diminuição da capacidade vital, do volume corrente e da capacidade pulmonar total. Portanto, a fraqueza muscular respiratória tem sido correlacionada com incidências mais elevadas de complicações pulmonares pós-operatórias. Tais intercorrências são particularmente importantes porque aumentam o tempo total de hospitalização, o tempo de permanência na Unidade de Terapia Intensiva, o tempo de ventilação mecânica e a morbimortalidade associada ao procedimento cirúrgico (21-23).

A forte relação entre algumas complicações cirúrgicas importantes com o uso do aparato extracorpóreo e a manipulação da aorta ascendente durante a manobra de clampeamento para canulação arterial, levou ao desenvolvimento da CRM sem CEC, uma tentativa de oferecer um procedimento menos invasivo e melhores resultados cirúrgicos em longo prazo (4, 5).

A técnica cirúrgica sem CEC é praticada em todo o mundo desde 1995, mas somente em 2002 passou a ser realizada em maior escala. Por meio dela, a equipe cirúrgica pode executar as anastomoses necessárias enquanto o coração, batendo, é estabilizado através de dispositivos de sucção que possibilitam o seu adequado posicionamento. Dados recentes indicam que a CRM sem CEC representa de 20% a 25% dos procedimentos cirúrgicos de revascularização do miocárdio realizados no mundo (4, 24).

Os resultados cirúrgicos alcançados com as duas técnicas, com e sem CEC, parecem ser similares em 30 dias e 12 meses (6, 7, 25). No entanto, estudos com seguimento de longo prazo divergem quanto aos resultados obtidos em cinco anos. O *CORONARY Trial* (5), um ensaio clínico randomizado com 4.752 pacientes, não encontrou diferença significativa entre os resultados cirúrgicos das duas técnicas.

Em contrapartida, outro grande ensaio clínico randomizado, o *ROOBY Trial* (25), concluiu que a CRM sem CEC apresenta mortalidade mais elevada em cinco anos. Outro estudo, ainda mais recente, publicou os resultados da coorte coreana de CRM, incluindo 7.691 pacientes, que indicou desfechos significativamente melhores associados à CRM sem CEC (8).

Os estudos citados demonstram que o tema continua controverso, mas o consenso atual é de que as duas técnicas são similares e extremamente dependentes da experiência da equipe cirúrgica. Uma das limitações mais evidentes dos ensaios clínicos randomizados é que a grande maioria das instituições envolvidas nos estudos tem como referência o uso de CEC. Além disso, a CRM com CEC ainda é considerada a intervenção cirúrgica de revascularização padrão e, por sua frequência e importância, é uma das primeiras técnicas que um cirurgião cardiovascular aprende em sua formação. Desta forma, a abordagem atual para a escolha da técnica cirúrgica, seja com ou sem CEC, é baseada na preferência do cirurgião (4, 5, 8).

Os resultados controversos relacionados às duas técnicas cirúrgicas tornaram ainda mais relevantes os estudos dos fatores de risco pré-operatórios. Eles compõem os modelos matemáticos de predição de morte hospitalar que determinam os escores de risco cirúrgico, amplamente utilizados na prática médica. O profundo conhecimento e a análise criteriosa dos fatores de risco proporcionam uma melhor estratificação dos pacientes e o encaminhamento ao tratamento mais adequado.

2.2 Modelos Prognósticos

Devido ao grande número de intervenções coronarianas, o estudo prognóstico dos pacientes submetidos ao procedimento ganhou destaque na última década, especialmente com o desenvolvimento de escores de risco largamente utilizados na prática clínica. Em casos específicos, esses modelos de predição são empregados inclusive para indicar ou contraindicar a realização de procedimentos cardiovasculares, sejam cirúrgicos ou percutâneos (18, 19).

Os dois modelos de EuroSCORE (26, 27) somados ao STS Score (28) são os modelos de predição mais utilizados atualmente para estimar o risco de morte

hospitalar de pacientes encaminhados para cirurgia cardiovascular. Apesar da grande aplicação e confiança, estes escores apresentam limitações importantes, podendo subestimar ou superestimar o risco de acordo com a população estudada (29-31). Esses achados reforçam que o estudo dos fatores de risco permanece relevante e necessário (9, 10).

Entre os fatores de importância subestimada está a fragilidade. Apesar da prevalência significativa, da associação a piores desfechos pós-intervenção cardiovascular e das evidências recentes sobre seus impactos, a condição não é considerada pelos escores de risco cirúrgico (11). O mesmo ocorre com a anemia pré-operatória, fator de risco significativo para doenças cardiovasculares e diretamente associada ao aumento da mortalidade em cirurgias cardíacas (32).

Dos três escores de risco mais populares, apenas o EuroScore 2 apresenta uma variável associada à fragilidade, mais especificamente à capacidade funcional dos pacientes. A variável refere-se à baixa mobilidade e recebe a seguinte definição: comprometimento importante da mobilidade em decorrência de disfunção musculoesquelética ou neurológica. Ainda assim, diversos estudos têm reportado problemas relacionados com o poder preditivo deste escore (29).

2.3 Fragilidade

Com o sólido crescimento da população com mais de 60 anos nas últimas décadas, a demanda por serviços de saúde em decorrência de problemas cardiovasculares apresentou um crescimento igualmente expressivo, principalmente em países em desenvolvimento. Embora as doenças cardiovasculares sejam a causa de morte mais comum em todo o mundo, as estratégias cirúrgicas têm contribuído cada vez mais para o aumento da expectativa de vida dos cardiopatas (33).

O prolongamento da sobrevida, por sua vez, exige que os profissionais da saúde estejam preparados para tomar decisões terapêuticas direcionadas a pacientes de risco mais elevado. Tanto que a realização de cirurgias de revascularização do miocárdio em pacientes com alto risco e idade avançada já é

parte da rotina, bem como a operação de pacientes com doenças crônicas graves ou limitantes (30).

Em populações cirúrgicas, a idade é um fator independente de risco para complicações pós-operatórias, incluindo mortalidade. No entanto, em populações idosas bem selecionadas, os resultados cirúrgicos são muito bons e consistentes, evidenciando que o perfil de risco vai muito além da idade cronológica (34). A ampliação das indicações cirúrgicas nos últimos anos é explicada, em parte, pelo melhor conhecimento do perfil clínico dos cardiopatas, porém ainda existem lacunas no estudo destes fatores, principalmente quando relacionados com a capacidade funcional dos pacientes (35, 36).

Especialmente em pacientes mais debilitados ou com idade avançada, o estudo prognóstico representa um desafio ao esbarrar na limitação dos escores risco tradicionais, que não possuem um bom valor preditivo para grupos de risco elevado. Da mesma forma, a implementação de procedimentos valvulares transcateres, indicados para pacientes idosos e de risco cirúrgico proibitivo, evidenciou a necessidade de complementar a análise dos escores de risco da área cardiovascular com avaliações de fragilidade (10, 11).

Em linhas gerais, a fragilidade é uma síndrome geriátrica caracterizada pela diminuição da resiliência a agentes estressores externos em decorrência da deterioração de múltiplos sistemas fisiológicos (37). Costuma estar associada com perda de peso não intencional, fraqueza muscular, fadiga, lentidão e níveis diminuídos de atividade física. Como consequência, a pessoa acometida por fragilidade possui risco aumentado de morte quando submetida a determinados agentes estressores, como um procedimento cirúrgico de grande porte, por exemplo (11, 38).

A fragilidade ainda é considerada um conceito emergente na prática médica cardiológica, mesmo que o seu estudo seja amplo em populações geriátricas há vários anos. Na área cardiovascular, a importância como fator de risco é recente e provavelmente ainda possui valor subestimado (34). Apesar do grande potencial, a avaliação não é padronizada e pode se tornar complexa pelo número de variáveis necessárias para classificar um paciente. Alguns autores sugerem, inclusive, que

ferramentas baseadas em algoritmos matemáticos sejam criadas para avaliar a fragilidade de modo seguro e padronizado (12, 37).

Em contrapartida, está cada vez maior a busca por fatores de risco que isoladamente possam indicar com segurança a fragilidade de um paciente. Estudos recentes apresentaram resultados promissores sobre a capacidade funcional avaliada pelo grau de mobilidade do indivíduo. Cockburn e colaboradores, em 2015, reportaram que a baixa mobilidade é melhor do que outras ferramentas de avaliação de fragilidade para prever intercorrências em pacientes submetidos à correção valvar (13). A importância da mobilidade na avaliação da população geriátrica está bem estabelecida, mas ainda é pouco considerada na predição de risco para cirurgias cardíacas (13, 37, 39, 40).

2.4 Índice de Katz

Como relatado, um dos aspectos já estudados e relacionados com a fragilidade e com o risco aumentado de morbimortalidade pós-cirurgia cardíaca é o grau de mobilidade do paciente. Tendo em vista essa relação direta, o Índice de Katz passou a ter um papel de destaque em estudos prognósticos envolvendo intervenções cardíacas valvulares (11).

O índice desenvolvido por Katz e colaboradores em 1976 possibilita uma classificação simples e rápida da mobilidade dos pacientes com base na avaliação de seis parâmetros relacionados a atividades cotidianas básicas – autonomia para banhar-se, vestir-se, alimentar-se, higienizar-se, transferir-se e continência (41). Quando o paciente é totalmente dependente, seu Índice de Katz é igual a zero; quando o paciente é independente em todas as funções, o índice é igual a seis (11-14, 42).

A utilização do Índice de Katz em pacientes cardiopatas encaminhados para a cirurgia cardíaca, entretanto, ainda é baixa. Trabalhos recentes têm demonstrado que a avaliação das atividades cotidianas diárias pode representar um grande acréscimo para os estudos prognósticos na área cardiovascular. Em 2014, Puls e colaboradores publicaram resultados em que o Índice de Katz foi considerado um poderoso preditor independente para desfechos ruins em curto e longo prazo em

pacientes valvulopatas submetidos à intervenção para correção de estenose aórtica. Além disso, a sobrevida durante o seguimento clínico foi significativamente menor em pacientes com qualquer nível de limitação em suas atividades diárias (11).

Ainda que não tenha usado o mesmo critério que Puls e colaboradores (2014), Lee e colaboradores (2010) demonstraram que a fragilidade é um fator de risco independente para mortalidade hospitalar pós-cirurgia cardíaca (34). Complementarmente, Afalalo e colaboradores estabeleceram a velocidade de marcha em cinco metros como preditor de mortalidade em pacientes com mais de 75 anos submetidos a procedimento cardíaco. Estes mesmos autores, em um estudo subsequente, demonstraram que a utilização de escalas de fragilidade e de capacidade funcional melhoraram o desempenho dos escores cirúrgicos na predição de desfechos (43).

Em 2010, Lee e colaboradores propuseram a seguinte definição para fragilidade: qualquer deficiência no Índice de Katz, dificuldade de marcha ou diagnóstico prévio de demência (34). Puls e colaboradores (2014) demonstraram que o Índice de Katz isoladamente possuía melhor poder discriminatório na estratificação de risco de pacientes idosos submetidos ao implante valvular aórtico transcater (11). Essa constatação é particularmente importante por proporcionar uma definição simplificada para a avaliação de fragilidade ou incapacidade. Além de simples, a utilização do Índice de Katz é reprodutível, objetiva e possui muita aplicabilidade em um cenário de assistência em saúde cada vez mais complexo e dependente de modelos matemáticos de predição de risco.

2.5 Anemia

Outra condição associada diretamente à capacidade funcional dos pacientes é a presença de anemia no período pré-operatório, bastante prevalente em pacientes submetidos à cirurgia cardíaca e que afeta de forma significativa os resultados cirúrgicos (15, 37). Os fatores mais determinantes para o estabelecimento de um quadro anêmico são eritropoese inadequada, função renal diminuída e hemodiluição. Todos estes componentes patogênicos podem estar presentes em pacientes com doença coronariana (44).

A maior parte dos pacientes com doença cardíaca isquêmica encaminhados para a cirurgia de revascularização do miocárdio é formada por idosos. Na população geriátrica, a anemia pode ter prevalência de até 43% e geralmente está associada com a ocorrência de sarcopenia, alterações na medula óssea, disfunções hormonais, produção insuficiente de eritropoietina e resposta inflamatória prejudicada (45).

Além deste aspecto, grande parte dos pacientes com doença cardíaca acaba recebendo também o diagnóstico de anemia causada por doença crônica. Este tipo de anemia é caracterizado por ativação imunológica aguda ou crônica e faz parte de uma síndrome inflamatória sistêmica. Ao combater infecções microbianas, o sistema imunológico acaba produzindo uma série de citocinas (Fator de Necrose Tumoral α , Interleucina-1 e Interleucina-6) que estão associadas à redução da disponibilidade de ferro no organismo e, conseqüentemente, com alterações na hematopoese (46, 47).

A anemia adquirida durante a internação hospitalar também é frequente em pacientes com doença arterial coronariana. Em 2011, Salisbury e colaboradores, após analisarem uma coorte com mais de 17 mil pacientes internados em decorrência de infarto agudo do miocárdio, identificaram uma incidência de 57% de anemia adquirida no período de internação. Os pesquisadores verificaram ainda que o desenvolvimento de anemia intra-hospitalar estava relacionado a fatores como idade, sexo feminino, doença renal, choque cardiogênico e uso extensivo de terapias antiplaquetárias e de anticoagulação (48).

A anemia pré-operatória é um reconhecido fator de risco para morbidades e para mortalidade perioperatória. Alguns estudos reforçaram a importância da condição como preditora independente de mortalidade pós-cirurgia de revascularização do miocárdio (32, 49). Adicionalmente, níveis diminuídos de hemoglobina no período pré-operatório também foram associados ao desenvolvimento de insuficiência renal no pós-operatório de revascularização cirúrgica (50, 51).

A realização de atividades diárias está diretamente ligada à capacidade de se exercitar, e isso depende de fatores diversos como idade, massa muscular, níveis de hemoglobina e função renal (17). Por ser uma condição debilitante, a anemia pode

impactar no grau de mobilidade do paciente e conseqüentemente no Índice de Katz. Desta forma, a avaliação da relação entre anemia e a capacidade do indivíduo de realizar tarefas diárias pode ser muito importante para caracterizar de forma mais efetiva e segura um paciente que apresenta algum grau de fragilidade (16, 17).

No entanto, os fatores que influenciam na capacidade de realizar exercícios físicos durante a reabilitação cardíaca e como eles afetam os pacientes com doença arterial coronariana permanecem incertos. A realização de estudos que busquem compreender essas interações são, portanto, necessários para melhorar a prática assistencial vigente.

3 OBJETIVOS

3.1 Objetivo Geral

O objetivo geral deste trabalho foi avaliar o impacto da fragilidade e da anemia pré-operatória sobre os desfechos hospitalares de pacientes submetidos à cirurgia de revascularização do miocárdio.

3.2 Objetivos Específicos

- Classificar os pacientes em frágeis e não-frágeis pelo Índice de Katz;
- Avaliar a associação da fragilidade com mortalidade hospitalar, MACCE e tempo de internação pós-procedimento;
- Avaliar a associação da anemia pré-operatória com mortalidade hospitalar, MACCE e tempo de internação pós-procedimento;
- Avaliar a capacidade preditiva dos escores de risco cirúrgicos quando utilizados isoladamente;
- Avaliar a capacidade preditiva dos escores de risco cirúrgico quando utilizados em associação com a fragilidade e a anemia pré-operatória;
- Comparar as capacidades preditivas dos escores de risco cirúrgico isolados e associados com a fragilidade e com a anemia.

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5 ARTIGO**Frailty and preoperative anemia are predictors of worst in-hospital outcomes after coronary artery bypass grafting**

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ABSTRACT

Background: CABG is the most performed cardiovascular surgery in the world, being the standard treatment for complex coronary artery disease. However, the surgical risk prediction still has important gaps. In this context, frailty and preoperative anemia may have an important role in a better risk prediction. Our main objective was evaluated the impact of frailty and preoperative anemia on post-CABG in-hospital outcomes. **Methods:** a cohort of consecutive patients undergoing isolated CABG was assembled from 2013 to 2017. Frailty was defined as any impairment in Katz Index. Of 1508 patients, 126 (8.4%) were frail. Baseline characteristics and outcomes were compared by univariate analysis. Multivariate regression models were applied for adjusted analysis of outcomes. The predictive accuracy of the regression models was accessed by ROC curves. The additional predictive accuracy of frailty and anemia, when associated with surgical risk scores, was analyzed by ROC curves comparison with DeLong test. **Results:** Frail patients were older, were more likely to be female, and had more associated comorbidities. Frailty was an independent predictor of in-hospital mortality (OR 5.55, 95%CI 1.92-16.06, $p = 0.002$) and MACCE (OR 5.60, 95%CI 1.93-16.2, $p = 0.001$). Additionally, frailty was associated with longer hospital stay after CABG (B 4.61, 95%CI 2.12 - 7.10, $p < 0.001$). Preoperative anemia was also an independent predictor of mortality (OR 2.23, 95%CI 1.08-4.61, $p = 0.029$) and MACCE (OR 2.43, 95%CI 1.20-4.95, $p = 0.014$). When associated with surgical risk scores, frailty and anemia improved the accuracy of the scores for mortality (EuroScore1 AUC = 0.70 x EuroScore1 Associated AUC = 0.77, $p = 0.035$ - EuroScore2 AUC = 0.71 x EuroScore2 Associated = AUC 0.77, $p = 0.049$). **Conclusions:** Frailty and preoperative anemia are independent predictors of in-hospital mortality and MACCE post-CABG. Frailty was also a strong predictor of longer hospital stay. The association of frailty and anemia with surgical risk scores showed better predictive accuracy than isolated scores. The frailty screening by the Katz Index improves risk assessment for isolated CABG, and if associated with anemia, it may identify a subgroup of patients who may benefit from preoperative optimization.

Key Words: frailty, anemia, CABG, EuroScore, mortality, MACCE, hospital discharge

INTRODUCTION

Every year there are 16 million deaths associated with cardiovascular diseases worldwide. Coronary artery disease has the highest prevalence and is directly associated with high risk of death and worst quality of life (1). Since the 1960s, the standard treatment for complex ischemic coronary diseases is the Coronary Artery Bypass Grafting (CABG), the most commonly performed cardiovascular surgical procedure in the world (2).

The increase in the life expectancy of the population also expanded the indication of surgical interventions in patients of advanced age groups and with associated comorbidities. To know the risk profile of these patients is mandatory, in order to obtain good surgical results. For this reason, surgical risk scores were developed to estimate the risk of death associated with cardiovascular surgery. Now these prognostic models are used in large scale and, in specific cases, are even applied to support the indication or contraindication of surgical procedures (3-7). However, the scores have important limitations and poor predictive power in some subgroups of cardiac patients. Because this, making continuous improvement of cardiovascular prognostic models is critical (8, 9).

The emergence of transcatheter valve implantations in elderly patients with prohibitive surgical risk demonstrated the need to complement the prognostic studies with some kind of frailty assessment. This condition is defined as a geriatric syndrome characterized by the decrease of resilience to stressors caused by the deterioration of multiple physiological systems, being related to greater risk of cardiovascular death (10, 11). Despite it is great predictive potential, frailty assessments are not standardized and some are too complex to be introduced into the health care routine (12, 13).

In this context, the search for risk factors that may indicate if a patient is frail and has a high surgical risk gained prominence more recently. Studies have demonstrated promising results in assessing the degree of mobility through the Katz

Index of Independence in Activities of Daily Living (ADL) as marker of frailty and, consequently, a predictor of post-cardiac surgery risk of death (11, 14-17).

The preoperative anemia also is associated with worst outcomes. Anemia is a debilitating condition and influences the patients' physical ability, mobility, and ability to perform their daily living activities (18). The degree of mobility and preoperative anemia are considered as emerging surgical risk factors and require new studies that may establish their importance as determinants in prognostic studies (18, 19). The goal of this study was to evaluate the impact of frailty – classified by the Katz Index – and the preoperative anemia on in-hospital outcomes of a cohort of 1508 patients submitted to isolated CABG.

METHODS

Patient Population

We identified and included consecutively all patients undergoing isolated CABG at the São Francisco Hospital of Santa Casa de Misericórdia, Porto Alegre, Rio Grande do Sul, Brazil, between January 2013 and December 2017. In this period were performed 2834 cardiovascular surgeries, including isolated CABG, CABG associated with valve replacements, isolated valve replacements, surgery of aorta and other associations of major surgeries. Only the patients undergoing isolated CABG were included, totalizing 1508 patients.

Ethical Aspects

The study protocol was approved by the Research Ethics Committees of the Santa Casa de Misericórdia of Porto Alegre and the Universidade Federal de Ciências da Saúde de Porto Alegre.

Data collection and variable selection

The data used in this study were obtained through the Cardiovascular Surgical Registry of the Hospital São Francisco. Created in 2010, the registry stores pre, trans, and postoperative variables. In all, there are 96 variables prospectively assessed. The data are collected and tabulated by trained cardiovascular scientists

who follow a pre-established standard of definitions and classifications of Society of Thoracic Surgery (STS). From 2013 to 2017, the percentage of missing data did not exceed 1% in any of the variables.

The preoperative variables considered for the study were: gender, age, weight, hypertension, diabetes *mellitus*, myocardial infarction, renal impairment, creatinine, chronic obstructive pulmonary disease, cerebrovascular disease, peripheral artery disease, documented episode or current atrial fibrillation, pulmonary artery pressure, left ventricular ejection fraction, heart failure NYHA Class III - IV, hemoglobin, unstable angina, previous cardiovascular surgery, previous percutaneous coronary intervention, EuroScore 1, EuroScore 2, frailty and anemia.

Frailty markers were the Katz Index of Independence in ADL (20, 21) (stratification variable) and preoperative anemia (secondary marker). The Katz Index was the only variable collected retrospectively, and for this, three trained researchers accessed the electronic records of each patient, collect and tabulate the data. The Katz Index was easily obtained through the preoperative evaluations notes of the physical therapy, nursing and medical teams. It was possible to collect the Katz Index from all patients in the study.

In addition to the value attributed to the Katz Index, each of the six items that compose the index was collected and tabulated individually: bathing (bathes self completely or needs help only a single part of the body), dressing (gets clothes from closets and puts on clothes complete), toileting (goes to toilet, gets on and off, clean genital area without help), transferring (moves in or out bed or chair unassisted), continence (exercise complete self-control over urination or defecation) and feeding (gets food from plate into mouth without help). Based on these activities of daily living, patients receive scores from 0 (fully dependent) to 6 (fully independent). For this study, the patients were classified into two groups according to the Katz Index: scores from 0 to 5 (Frail Group) and score equal to 6 (Non-Frail Group).

The anemia was defined based on the preoperative hemoglobin value, being considered the one closest to the surgery. Following the recommendations of International Federation of Clinical Chemistry (22), we adopted the local reference values based on a population study for the State of Rio Grande do Sul. Men with

hemoglobin values below 12.8 g / dL and women with values below 11.6 g / dL were considered anemic (23).

The trans-operative characteristics evaluated included emergency or urgency surgery, use of cardiopulmonary bypass, cardiopulmonary bypass time, aortic clamping time, use of internal thoracic artery graft, number of coronary vessels with significant obstructions (stenosis > 70%), stenosis > 50% in the left main coronary artery, number of distal anastomoses performed in the intervention, complete revascularization according to the preoperative plan and need for conversion the off-pump to on-pump technique.

Surgical Technique

Most patients underwent on-pump CABG (76.1%). The option to operate with or without extracorporeal support was performed by the surgeon according to the anatomical characteristics of the coronary stenosis, the left ventricular function and the approval of the health insurance. The cardioplegia developed by del Nido (24) was used to preserve the heart during on-pump surgeries. The solution was cooled to 4°C and delivered anterograde to the heart. All the surgeries were performed in the Hospital São Francisco, in the same operation rooms and by the same team of surgeons and perfusionists.

Outcomes

The primary outcomes of this study were in-hospital mortality, major cardiovascular and cerebrovascular events (MACCE – association of death, acute myocardial infarction, stroke and or new revascularization), and length of hospital stay after the surgery. The need for new revascularization, stroke, acute myocardial infarction, bleeding, pleural effusion, respiratory infection and sepsis were the secondary outcomes.

Statistical analysis

The categorical variables were described by absolute numbers and frequencies. The continuous variables were described by mean and standard deviation. The normality evaluation was performed by analysis of asymmetry,

kurtosis and Shapiro-Wilk test. The preoperative, transoperative and postoperative in-hospital outcomes were compared by univariate analysis with Pearson's Chi-square test, for categorical variables, and the T-Test for Independent Samples, for continuous variables.

Variables identified as statically associated and clinically relevant with outcomes ($p \leq 0.10$) in the univariate statistical tests were included in the adjusted multivariate models. The collinearity analysis was performed using the correlation matrix ($r \geq 0.3$). The association between frailty, anemia and in-hospital outcomes were examined using binary logistic regression (mortality and MACCE) and multiple linear regression (length of hospital stay). The predictive accuracy of each model was evaluated using ROC curves based on predicted probabilities obtained through the regression models.

The DeLong Test for comparison of ROC curves was used to evaluate the predictive accuracy of the surgical risk scores (EuroScore 1 and EuroScore 2), isolates and associates with frailty and anemia. Area under the curve and exact binomial confidence interval were used to describe the prediction curves.

Multivariate analyzes, as well as univariate analyzes and ROC curves comparison, were interpreted based on a significance level of 5% ($p \leq 0.05$). Statistical analysis was performed with SPSS software version 21 (IBM). The authors of the study had access to all data and take full responsibility for the integrity of the analyzes and information obtained. In the same way, they assume knowledge and agreement with the final writing.

RESULTS

Baseline Characteristics

Between January 2013 and December 2017, a total of 1508 patients underwent isolated CABG in our institution. The Katz Index of Independence in ADL was used as the primary marker of frailty and as a parameter for stratification the patients in two groups: "Non-Frail" (patients with a Katz Index equal 6, $n = 1,382$, 91.7%) and "Frail "(Patients with Katz Index between 0 and 5, $n = 126$, 8.3%). Among the frail patients, the activity of daily living compromised with greater

prevalence was transferring (96, 76.2%), followed by the bathing (85, 67.5%) and the toileting (73, 57.9%). In addition, the secondary marker of frailty of this study, preoperative anemia, was identified in 519 (34.4%) patients.

Baseline preoperative characteristics are presented in **Table 1**. The frail patients were older than the non-frail patients (68 ± 9.1 years vs 62 ± 9.5 years; $p < 0.001$), more likely to be female and had more associated comorbidities, including diabetes, chronic obstructive pulmonary disease, myocardial infarction, heart failure NYHA Class III - IV, cerebrovascular disease, renal impairment and anemia. The prevalence of previous cardiovascular surgery in the frail patient group was also higher, whereas previous coronary angioplasty was more frequent in non-frail patients. The two surgical risk scores assessed in this study (EuroScore 1 and EuroScore 2) were higher in frail patients, indicating a higher surgical risk profile in frail patients.

With regard to the surgical procedure of revascularization, the frail patients were operated more frequently in an emergency or urgency situations and received less internal thoracic artery graft. The use of cardiopulmonary bypass, number of vessels with important stenosis and number of anastomoses performed showed no differences, demonstrating that the procedures presented similar complexity (Table 2).

Unadjusted In-Hospital Outcomes

The univariate analysis of the in-hospital outcomes showed that stroke, acute myocardial infarction, respiratory infections, sepsis, MACCE and mortality had higher incidences in the frail patients (**Table 3**). In addition, these patients also had longer hospitalization stay, remaining on average more six days in the hospital.

In-Hospital Mortality

Unadjusted analysis: In the univariate analysis, the frailty was associated with higher in-hospital mortality (non-frail 2.5%, frail 15.9%, $p < 0.001$) – **Table 3**. Additionally, when the analysis of mortality was stratified in four groups according to the frailty and anemic status, the mortality rate for frail and anemic patients was 19.2%, while frail patients without anemia had 11.3%, non-frail patients with anemia

had 4.7% and non-frail and non-anemic patients had 1.5% of mortality ($p < 0.001$) – **Figure 1**.

Adjusted analysis: the variables considered to build the mortality logistic regression model were significantly associated with the outcome by univariate analysis and included: female sex, age, diabetes, atrial fibrillation, cerebrovascular disease, hypertension, heart failure with NYHA Class III - IV, chronic obstructive pulmonary disease, pulmonary artery pressure, myocardial infarction, hemodialysis, anemia, on-pump technique, no use of internal thoracic artery graft, anemia and frailty.

The results obtained by logistic regression, adjusted for comorbidities, showed that frailty was an independent predictor of risk for in-hospital mortality (OR 5.55, 95%CI 1.92-16.06, $p = 0.002$). The preoperative anemia was also classified as an independent predictor of death (OR 2.23, 95%CI 1.08-4.61, $p = 0.029$). Additionally, when associates, frailty and anemia showed better predictive ability with an even greater odds ratio for the occurrence of hospital mortality (OR 7.92, 95%CI 3.26-19.20, $p < 0.001$). Hemodialysis, chronic obstructive pulmonary disease and on-pump technique were also predictors of mortality. The regression model showed predictive accuracy of 81.1% and is detailed in the **Table 4**.

In-Hospital MACCE

Unadjusted analysis: frailty was associated with higher MACCE (non-frail 8.0%, frail 30.2%, $p < 0.001$) – Table 3. Additionally, in the same way of mortality, when the analysis of MACCE was stratified in four groups according to the frailty and anemic status, the MACCE rate for frail and anemic patients was 32.9%, while frail patients without anemia had 26.4%, non-frail patients with anemia had 10.1% and non-frail and non-anemic patients had 6.9% of MACCE ($p < 0.001$) – **Figure 2**.

Adjusted analysis: the variables considered to build the MACCE logistic regression model were significantly associated with the outcome by univariate analysis and included: female sex, age, diabetes, atrial fibrillation, cerebrovascular disease, heart failure NYHA Class III - IV, chronic obstructive pulmonary disease, pulmonary artery pressure, peripheral artery disease, myocardial infarction,

creatinine clearance, on-pump technique, no use of internal thoracic artery as graft, anemia and frailty.

The logistic regression, adjusted for comorbidities, showed the frailty as an independent risk predictor for in-hospital MACCE (OR 5.60, 95% CI 1.93 - 16.2, $p = 0.001$). Preoperative anemia was also classified as an independent predictor (OR 2.43, 95% CI 1.20 - 4.95, $P = 0.014$). And when associated, frailty and anemia were a risk predictor with an even greater OR for MACCE (OR 8.23, 95% CI 3.42 - 19.8, $P < 0.001$). Chronic obstructive pulmonary disease and the on-pump technique were also characterized as predictors of MACCE. The regression model showed predictive accuracy of 80.4% (Table 5).

Hospital Stay After CABG

Unadjusted analysis: frailty was also associated with longer post-CABG hospital stay in the unadjusted analysis. While the mean time of hospitalization after the surgery of non-frail patients was 10 days, the mean time of hospitalization of fragile patients was 16 days ($p = 0.009$) - **Table 3**.

Adjusted analysis: the longer hospital stays associated, by univariate analysis, with the frail patients was confirmed by multiple linear regression adjusted for comorbidities. The adjusted analysis showed that frail patients tend to remain hospitalized four days longer than non-frail patients (B 4.61, 95%CI +2.12 to +7.10, $p < 0.001$). On the other hand, anemia did not have a significant impact on the length of hospital stay post-CABG (B -0.93, 95%IC -0.244 to -0.58, $p = 0.228$). Female sex, diabetes, hemodialysis and time of cardiopulmonary bypass also showed a significant impact on the length of hospital stay – **Table 6**.

Predictive accuracy of Surgical Risk Scores, Frailty and Anemia

The analysis of the predictive accuracy of the surgical risk scores showed that EuroScore 1 and EuroScore 2 isolated showed significantly lower accuracy than when associated with frailty and anemia. While EuroScore 1 presented an area under the curve of 0.70, the association of EuroScore 1, frailty and anemia presented an area under the curve of 0.77 ($p = 0.035$). The EuroScore 2 had similar results and presented an area under the curve of 0.71, but when associated with frailty and

anemia also presented a higher area under the curve of 0.77 ($p = 0.049$). These results showed that the association of surgical risk scores with the frailty and anemia improved significantly the predictive accuracy of the EuroScore 1 and the EuroScore 2 (**Figure 3**).

DISCUSSION

Our study showed the preoperative anemia and frailty, as measured by the Katz Index, are both independent predictors for in-hospital mortality and MACCE after isolated CABG. Frailty was also associated with longer hospital stay. When utilized together with commonly used surgical risk scores, anemia and frailty improved the predictive ability of the scores, added predictive accuracy.

The frailty still represents an emerging concept and therefore its classification is heterogeneous and still does not have standardization, being a characteristic that can be verified by several different tools (12, 13, 25). The main concepts of frailty usually include a number of clinical features – loss of muscle mass, low levels of activity and endurance are examples of frequent characteristics. Given that the association between dependence to perform one or more activities of daily living and frailty has already been well demonstrated previously (11-13), we chose to use the Katz Index of Independence in ADL to identify and classify frail patients. The index is widely accepted and used since the 1970s to measure the degree of dependence, especially in patients with more advanced age (20, 21, 26).

At the same time, studies evaluating the impact of frailty on patients undergoing transcatheter aortic valve implantation (TAVI) played an important role in stimulating the observation of the condition in patients undergoing conventional heart surgery (27, 28). In 2014, Sündermann *et al.*, evaluating 450 patients undergoing cardiac surgery, concluded that frailty is an independent predictor of risk for short- and medium-term mortality after the surgical procedure. To identify frail patients, the researchers used the Comprehensive Assessment of Frailty and the Frailty Predicts Death One Year After Elective Cardiac Surgery Test (28). Sapehri *et al.*, also in 2014, concluded that frail patients, identified by several different tools, are at higher risk of death, as well as functional decline and increased risk of MACCE after cardiac surgery (8). More recently, in 2018, Reichart *et al.* evaluated, through the Clinical

Frailty Scale, the impact of frailty on the occurrence of death after CABG. The researchers analyzed the data of 6,156 patients submitted to surgical revascularization and concluded that the frailty predicts mortality in the short and medium term in patients submitted to isolated CABG (25).

The present study also found similar results to the studies cited so far. However, our investigation had the additional analysis of the impact of preoperative anemia on post-CABG outcomes. The results showed that anemia is also a predictor risk of in-hospital mortality and MACCE. Because it is a debilitating condition and affects the functional capacity of patients, anemia is a factor that enhances frailty. The adjusted mortality analysis showed that frail and anemic patients had a higher *Odds Ratio* for death and MACCE than non-anemic frail patients and only anemic patients. We also identified that anemia and frailty improved the predictive ability of risk surgical scores for in-hospital mortality.

Previous results have been showed that surgical risks scores have poor accuracy for specifically groups of patients undergoing to CABG, including the elderly population (29-31). Because this, the better predictive accuracy associated with the EuroScore 1 and EuroScore 2 when the scores were linked with frailty and anemia it was a very important finding. The future perspectives certainly should include new studies for improve the prognostic models of cardiovascular surgery with the addition of emergent risk factors as frailty and anemia.

We were able to confirm that frail patients have a more severe risk profile. It was possible to verify that they were older and had a higher prevalence of comorbidities such as diabetes, chronic obstructive pulmonary disease, heart failure NYHA Class III - IV, previous myocardial infarctation, cerebrovascular disease and anemia. The prevalence of previous cardiovascular surgery in the group of frail patients was also higher. In addition, the two surgical risk scores assessed in this study were higher in frail patients. However, these differences between the groups did not impact the results obtained, since they were corrected and mitigated by performing specific and adjusted multivariate analysis models for the outcomes of interest (in-hospital mortality and MACCE and length of hospital stay).

With the perform of this work, we can demonstrate the impact that a simple classification of frailty, performed only with the Katz Index, can have on the prediction

of post-CABG in-hospital outcomes. Unlike other tools used to measure and classify frailty, the index only assesses patients' ability to perform six basic daily living activities - bathing, dressing, toileting, transferring, continence, and feeding. Independent patients had a Katz Index of 6 and were considered non-frail. Dependent patients had a Katz Index between 0 and 5 and were considered frail. In the same way, as previous studies (11, 12, 32), we also found a strong association between frailty classified by the Katz Index and the occurrence of worse post-procedure outcomes.

The results obtained with this study lead us to question whether revascularization surgery is always justified in frail patients, especially for the patients with associated preoperative anemia and high surgical risk. The results presented by our group and by other researchers in previous studies indicate that patients with this risk profile are operated regularly within the routines of cardiovascular surgery services, even though the surgical results are significantly worse. In addition, these patients are likely to receive inaccurate information about their real risk when only the surgical risk score is considered. It is important that the teams involved in surgical care to mitigate the risks associated with frail patients through the adequacy of healthcare protocols. Our study suggests the use of programs to improve the mobility of frail patients safely and supervised by a multidisciplinary team. In addition, for elective patients, measures may be taken to correct anemia prior to cardiovascular surgery. However, these preoperative measures should be tested in randomized clinical trials prior to wide implementation.

The main limitation of the study was the retrospective collection of the Katz Index. However, the collection of the index was possible for all patients with safety and precision because the data was produced prospectively and described in the electronic hospital register. In this way, only the collection of the Katz Index was retrospective. All other variables were prospectively collected from a standardized institutional register and fed by a single team of researchers. Although the study involved a single center, which may limit the number of patients analyzed, this delimitation allowed all patients to be operated on the same operation rooms, with the same technological support and by the same surgical team. All patients received exactly the same care and were submitted to the same protocols of medical care,

nursing, physical therapy and nutrition. In addition, rigorous statistical methods were adopted and the data were extensively audited and reviewed. The rate of missing of data did not exceed 1% in any of the study variables, guaranteeing the performance of the statistical processes through tests with great statistical power of determination.

CONCLUSIONS

In conclusion, we were able to demonstrate that the preoperative classification of frailty through the Katz Index for Independence in ADL showed an association with in-hospital mortality, MACCE and longer hospitalization stay after the surgery. We have identified the risk-enhancing role that preoperative anemia exerts specially on frail patients. In addition, we have found that the association between frailty and anemia improves the predictive accuracy of EuroScore 1 and EuroScore 2 for in-hospital mortality. To identify the most severe patients enables them to be better informed about the procedure for which they were referred and also allows the health multidisciplinary team apply the best care protocols and lead the patient to surgery at the most favorable time, considering the risk scores, the evaluation of the frailty and the preoperative anemia.

LIST OF ABBREVIATIONS

ADL	Activity of Daily Living
AUC	Area Under the Curve
CABG	Coronary Artery Bypass Grafting
CI	Confidence Interval
CPB	Cardiopulmonary Bypass
MACCE	Major Cardiovascular and Cerebrovascular Events
NYHA	New York Heart Association
OR	<i>Odds Ratio</i>
ROC	Receiver Operating Characteristic
TAVI	Transcatheter Aortic Valve Implantation

DECLARATIONS

ETHICAL APPROVAL

The current study was submitted for the Ethical Committee of Santa Casa de Misericórdia de Porto Alegre and had the official approval in January 2007. The Certificate of Presentation for Appreciation (CAAE) is 62758616.8.000.5335 and the number of study approval document is 1.888.166.

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CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from corresponding author on reasonable request.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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AUTHORS' CONTRIBUTION

Álvaro Machado Rösler – Made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data and drafting the manuscript.

Gabriel Constantin – Made substantial contributions to acquisition of data and to revising it critical in manuscript content.

Pedro Nectoux - Made substantial contributions to acquisition data.

Dionatan Lima Borges - Made substantial contributions to acquisition data.

Jonathan Fraportti - Made substantial contributions to acquisition of data and to revising it critical in manuscript content.

Fernando Antônio Lucchese – Made substantial contributions to revising it critical in manuscript content.

Mauro Ricardo Nunes Pontes - Made substantial contributions to conception and design and to revising critically the manuscript content.

Pedro Dal Lago - Made substantial contributions to conception and design, revising critically the manuscript content and given the final approval of the version to be published.

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ENDNOTES

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Table 1. Preoperative Patient Characteristics

Variables	Non-frail (n = 1382)	Frail (n = 126)	p
Female sex	383 (27.7%)	46 (36.5%)	0.036
Age (years)	62.3 ± 9.1	68.0 ± 9.5	<0.001
Weight (Kg)	77.8 ± 13.2	76.1 ± 13.5	0.166
Hypertension	1168 (84.5%)	116 (92.1%)	0.023
Diabetes	556 (40.2%)	63 (50%)	0.033
Myocardial infarctation	528 (38.2%)	69 (54.8%)	<0.001
Unstable angina	136 (9.8%)	17 (13.5%)	0.194
Renal impairment	130 (9.4%)	25 (19.8%)	<0.001
Creatinine clearance	78.8 ± 29.9	68,1 ± 31.5	<0.001
Hemodialysis	35 (2.5%)	6 (4.8%)	0.148
Smoking	779 (56.4%)	66 (52.4%)	0.388
Chronic obstructive pulmonary disease	80 (5.8%)	8 (6.3%)	0.797
Cerebrovascular disease	100 (7.2%)	18 (14.3%)	0.005
Peripheral artery disease	53 (3.8%)	11 (8.7%)	0.009
Atrial fibrillation	55 (4.0%)	13 (10.3%)	0.001
Left ventricular ejection fraction (%)	60,6 ± 12,4	56,9 ± 14,0	0.005
Heart Failure NYHA Class III - IV	383 (27.7%)	47 (37.3%)	0.022
Anemia	446 (32.3%)	73 (57.9%)	<0.001
Previous cardiovascular surgery	22 (1.6%)	5 (4.0%)	0.068
Previous coronary angioplasty	323 (23.4%)	19 (15.1%)	0.033
EuroScore 1	3.19 ± 3.41	6.73 ± 7.11	<0.001
EuroScore 2	1.66 ± 1.40	2.49 ± 2.30	<0.001

Table 2. Operative Characteristics

Variables	Non-frail (n = 1382)	Frail (n = 126)	<i>P</i>
Emergency or Urgency	37 (2.7%)	8 (6.3%)	0.048
On-pump CABG	1047 (75.8%)	101 (80.2%)	0.268
Cardiopulmonary bypass time (minutes)	79.6 ± 24.0	83.5 ± 24.9	0.139
Aortic clamping time (minutes)	64.0 ± 20.2	66.1 ± 20.1	0.323
Internal thoracic artery graft	1273 (92.1%)	99 (78.6%)	<0.001
Coronaries with stenosis > 70%	3.3 ± 1.26	3.3 ± 1.23	0.944
Number of anastomosis	3.3 ± 1.25	3.2 ± 1.17	0.953
Complete revascularization	1338 (91.6%)	122 (96.8%)	0.970

Table 3. Unadjusted In-Hospital Outcomes

Variables	Non-frail (n = 1382)	Frail (n = 126)	<i>P</i>
Surgery conversion to on-pump	3 (0.2%)	0 (0%)	1.000
New revascularization	9 (0.7%)	1 (0.8%)	0.583
Stroke	54 (3.9%)	12 (9.5%)	0.003
Myocardial infarction	26 (1.9%)	7 (5.6%)	0.016
Bleeding	19 (1.4%)	0 (0%)	0.396
Pleural effusion	14 (1%)	1 (0.8%)	1.000
Respiratory infection	13 (0.9%)	7 (5.6%)	0.001
Sepsis	13 (0.9%)	4 (3.2%)	0.047
MACCE	110 (8.0%)	38 (30.2%)	<0.001
Length of hospital stay (days)	10.1 ± 10.5	16.2 ± 25.5	0.009
In-hospital death	35 (2.5%)	20 (15.9%)	<0.001

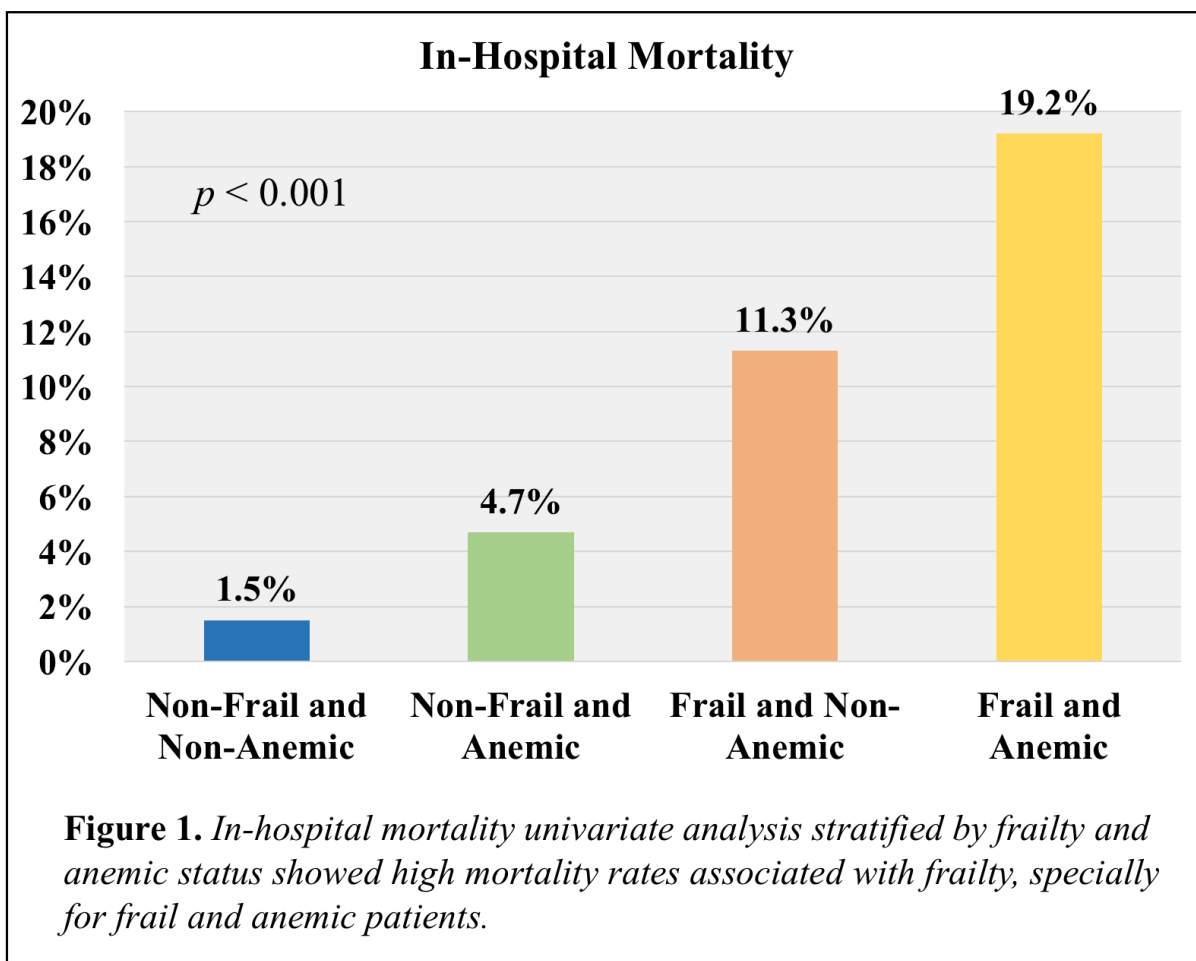


Table 4. Risk-Adjusted Impact of Frailty on In-Hospital Mortality

Preoperative and Operative Characteristics	OR	95% CI	P
Female Sex	1.50	0.81-2.75	0.190
Age	1.03	0.99-1.06	0.074
Diabetes	1.41	0.77-2.56	0.256
Atrial Fibrillation	1.98	0.78-5.06	0.149
Cerebrovascular disease	1.11	0.44-2.82	0.814
Hypertension	3.16	0.73-13.68	0.123
Heart failure NYHA Class III - IV	1.46	0.79-2.66	0.218
Pulmonary artery pressure	1.02	0.99-1.05	0.077
Peripheral artery disease	0.02	0.34-3.01	0.963
Myocardial infarctation	0.79	0.43-1.45	0.447
Hemodialysis	3.00	1.02-8.81	0.046
Chronic obstructive pulmonary disease	2.65	1.06-6.61	0.037
Frailty and Anemia	-	-	-
<i>Only Anemia</i>	2.23	1.08-4.61	0.029
<i>Only Frail</i>	5.55	1.92-16.06	0.002
<i>Frail and Anemia</i>	7.92	3.26-19.20	<0.001
No internal thoracic artery graft	0.63	0.30-1.32	0.221
On-Pump CABG	3.00	1.11-8.08	0.029

Predictive accuracy: ROC 81.1%, 95% CI 74.8%-87.4%, P < 0.001

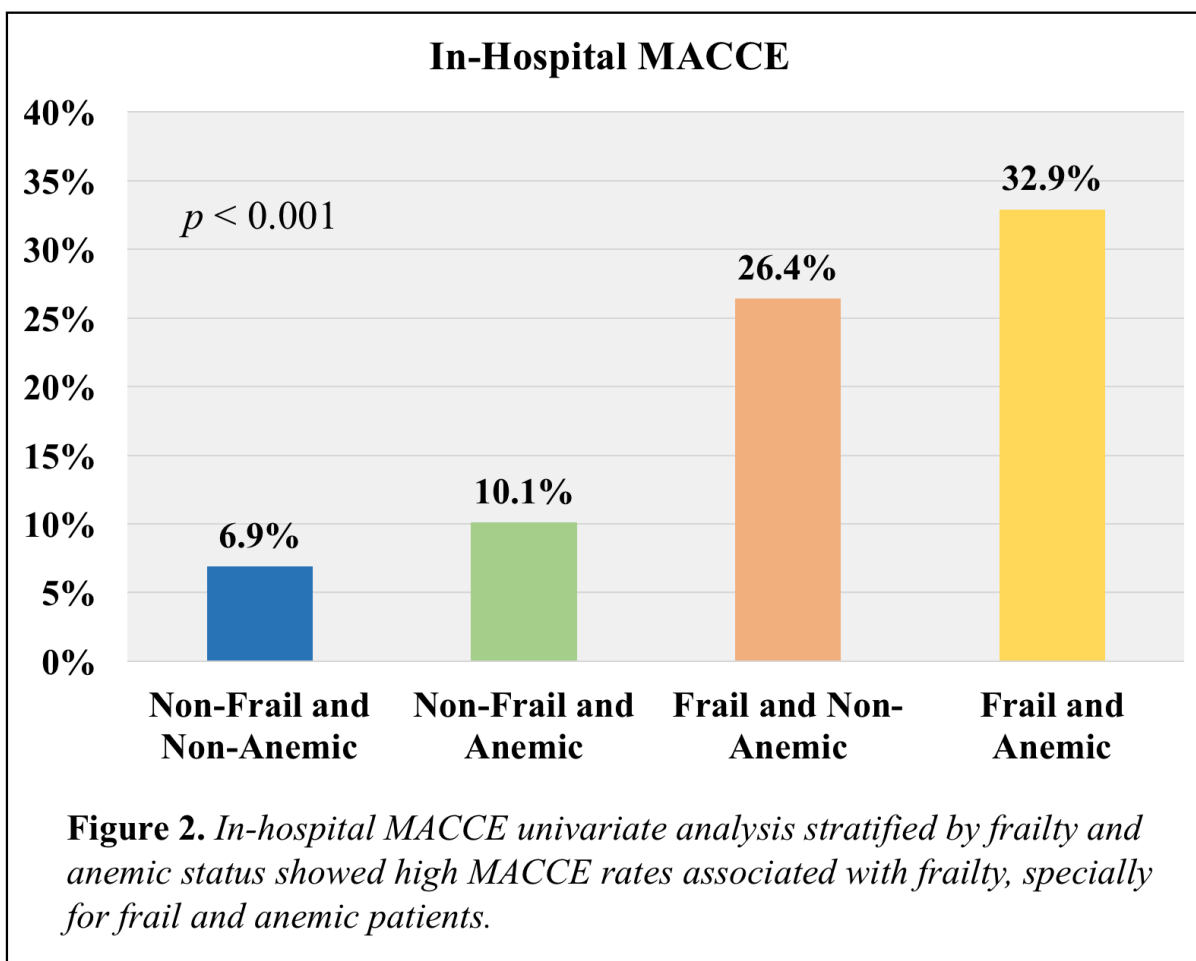


Table 5. Risk-Adjusted Impact of Frailty on In-Hospital MACCE

Preoperative and Operative Characteristics	OR	95% CI	P
Female Sex	1.48	0.81-2.71	0.202
Age	1.02	0.99-1.06	0.165
Diabetes	1.61	0.89-2.88	0.109
Atrial Fibrillation	1.97	0.78-4.97	0.149
Cerebrovascular disease	1.34	0.56-3.20	0.505
Heart Failure NYHA Class III - IV	1.45	0.79-2.65	0.228
Pulmonary artery pressure	1.02	0.99-1.05	0.075
Peripheral artery disease	1.47	0.55-3.92	0.432
Myocardial infarctation	0.76	0.42-1.39	0.388
Creatinine clearance	0.99	0.98-1.00	0.575
Chronic obstructive pulmonary disease	2.49	1.01-6.13	0.047
Frailty and Anemia	-	-	-
- Only Anemia	2.43	1.20-4.95	0.014
- Only Frail	5.60	1.93-16.2	0.001
- Frail and Anemia	8.23	3.42-19.8	<0.001
No internal thoracic artery graft	0.55	0.27-1.14	0.113
On-Pump CABG	3.19	1.18-8.58	0.022

Predictive accuracy: ROC 80.4%, 95% CI 74.1%-86.8%, P < 0.001

Table 6. Adjusted Analysis of Impact of Frailty on Hospital Stay

Preoperative and Operative Characteristics	B	95%CI	P
Female Sex	2.26	+0.67 to +3.84	0.005
Age	0.03	-0.05 to -0.12	0.450
Diabetes	1.47	+0.39 to +2.91	0.044
Atrial Fibrillation	1.83	-1.27 to -4.94	0.248
Cerebrovascular disease	1.68	-0.95 to -4.31	0.211
Hemodialysis	10.36	+5.55 to +15.18	<0.001
Renal impairment	1.24	-154 to +4.02	0.382
Pulmonary artery pressure	0.005	-0.08 to +0.09	0.909
Peripheral artery disease	-1.90	-5.40 to +1.60	0.287
Myocardial infarctation	-0.21	-1.65 to +1.21	0.766
Creatinine clearance	-0.20	-0.04 to +0.006	0.138
Chronic obstructive pulmonary disease	2.86	-0.24 to +5.97	0.071
Left ventricle eject fraction	-0.012	-0.047 to +0.045	0.681
On-Pump CABG	0.047	+0.018 to +0.076	0.001
Anemia	-0.93	-2.44 to +0.58	0.288
Frailty	4.61	+2.12 to +7.10	<0.001

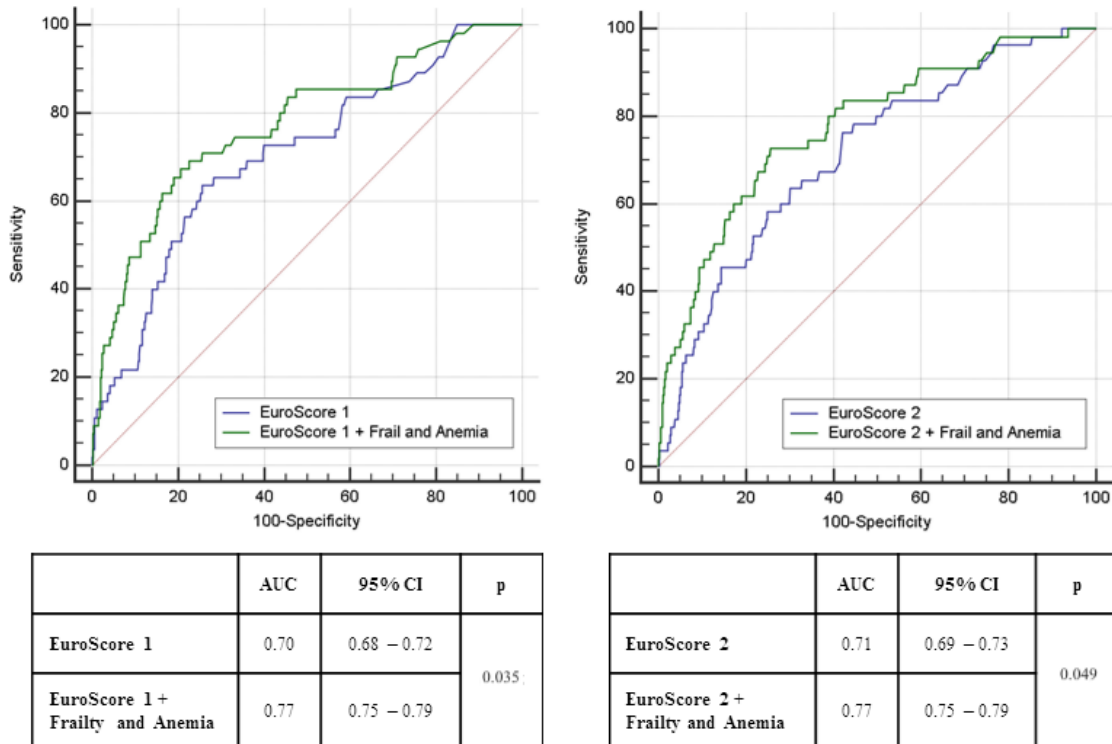


Figure 3. Receiver-operating characteristics curves of isolated surgical risk scores and association between score, frailty and anemia for predictive accuracy of in-hospital mortality. The ROC curves were compared by DeLong Test.

6 CONCLUSÃO GERAL

A realização deste trabalho demonstrou que a classificação pré-operatória da fragilidade através do Índice de Katz é simples e fácil de ser medida e implementada. O modelo de estratificação da fragilidade utilizado neste estudo, além de diferir de outras ferramentas mais complexas por considerar somente uma variável, emprega um índice vigente há décadas e largamente aplicado na avaliação pré-operatória de centros de referências. No entanto, sua importância e aplicação na área cardiovascular ainda é subestimada.

Na presente pesquisa, a fragilidade apresentou associação com maiores taxas de mortalidade hospitalar, eventos cardiovasculares e cerebrovasculares graves e maior tempo de internação. Pode-se observar que piores desfechos foram significativamente mais frequentes em pacientes frágeis com diagnóstico associado de anemia. Desta forma, também foi possível identificar o papel potencializador de risco que a anemia pré-operatória exerce sobre os pacientes frágeis.

Adicionalmente, verificou-se que a associação entre fragilidade e anemia melhorou a habilidade preditiva do EuroScore 1 e do EuroScore 2. Estes achados sugerem que tais modelos prognósticos poderiam ter melhores acurácias se associados à fragilidade e à anemia. A avaliação criteriosa do risco cirúrgico, além de permitir que os pacientes sejam melhor informados sobre o procedimento para o qual foram encaminhados, possibilita que a equipe de saúde adeque a atenção pré-operatória de pacientes com perfil clínico-cirúrgico de maior gravidade.

Embora o aumento da população idosa e a consequente ampliação das indicações cirúrgicas para pacientes com risco operatório mais elevado aumente a relevância e utilização de modelos prognósticos, estes ainda apresentam falhas, subestimando ou superestimando o risco cirúrgico para determinados subgrupos de pacientes. Por esta razão, não nos causou surpresa que variáveis não contempladas pelos escores de risco cirúrgico tenham sido identificadas como preditoras independentes para mortalidade, MACCE e maior tempo de internação hospitalar, além de terem melhorado a capacidade de predição de modelos consagrados.

7 ANEXOS

7.1 Carta de Aprovação do CEP

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DE MISERICORDIA DE PORTO
ALEGRE - ISCMPA



PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Impacto da mobilidade e da anemia pré-operatória na recuperação de pacientes submetidos à cirurgia de revascularização do miocárdio.

Pesquisador: Pedro Dal Lago

Área Temática:

Versão: 1

CAAE: 62758616.8.0000.5335

Instituição Proponente: ISCMPA

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.888.166

Apresentação do Projeto:

Trata-se de estudo de coorte observacional retrospectivo, consistira na inclusao de dados no registro cirurgico de revascularizacao do miocardio criado e abastecido pela Unidade de Pesquisa em Cirurgia Cardiovascular do Hospital Sao Francisco. O referido registro e mantido desde 2010 pelo Servico de Cirurgia Cardiovascular da Instituicao e inclui a coleta prospectiva de dados demograficos, clinicos, cirurgicos, laboratoriais, ecocardiograficos e de eventos adversos hospitalares. Com a realizacao do presente estudo, serao includas, de forma retrospectiva por meio da revisao dos prontuarios medicos, variaveis relacionadas ao grau de mobilidade (Indice de Katz) e as intercorrencias de carater respiratorio (tempo de ventilacao mecanica) e muscular (tempo para deambulacao). Os pesquisadores vinculados ao estudo farao a revisao dos prontuarios e incluirao no banco de dados do registro cirurgico de revascularizacoes do miocardio apenas os dados pertinentes a pesquisa.

Serão incluídos pacientes acima de 18 anos submetidos a cirurgia de revascularizacao do miocardio, isolada ou associada apenas a cirurgia aortica, entre janeiro de 2010 e dezembro de 2015 no Hospital Sao Francisco sob coordenacao do Servico de Cirurgia Cardiovascular da Instituicao.

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Continuação do Parecer: 1.888.166

Objetivo da Pesquisa:

Primário: Avaliar o impacto do grau de mobilidade e da presença de anemia na recuperação hospitalar de pacientes submetidos a cirurgia de revascularização do miocárdio.

Objetivo Secundário:

- Avaliar o valor preditivo do grau de mobilidade e da presença de anemia em relação a mortalidade hospitalar e outros eventos adversos graves pós-cirurgia de revascularização do miocárdio;- Avaliar o valor preditivo do grau de mobilidade e da presença de anemia em relação ao tempo de ventilação mecânica pós-CRM;- Avaliar o valor preditivo do grau de mobilidade e da presença de anemia em relação ao tempo necessário para o paciente deambular pós-CRM;- Identificar preditores de complicações pulmonares pós-CRM;- Avaliar possível inter-relação entre grau de mobilidade e presença de anemia.

Avaliação dos Riscos e Benefícios:

O presente não apresenta qualquer risco para o paciente tendo em vista o caráter puramente observacional. A identidade e a privacidade dos pacientes será preservada e o protocolo seguirá as diretrizes de boas práticas clínicas.

Os benefícios incluem uma melhor compreensão do risco ao qual os pacientes encaminhados para cirurgia de revascularização do miocárdio são submetidos. O estudo possibilitará uma melhor compreensão sobre o impacto do grau de mobilidade e da presença de anemia sobre os resultados da cirurgia citada.

Comentários e Considerações sobre a Pesquisa:

vide conclusão

Considerações sobre os Termos de apresentação obrigatória:

Adequados.

Recomendações:

Nenhuma

Conclusões ou Pendências e Lista de Inadequações:

A presente pesquisa encontra-se dentro das normas de pesquisa em seres humanos vigentes em nosso País. Pode contribuir com maior conhecimento sobre os riscos para desfecho após cirurgia de revascularização miocárdica em nosso meio.

Considerações Finais a critério do CEP:

Após avaliação do protocolo acima descrito, o presente comitê não encontrou óbices quanto ao

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desenvolvimento do estudo em nossa Instituição e poderá ser iniciado a partir da data deste parecer.

Obs.: 1 - O pesquisador responsável deve encaminhar à este CEP, Relatórios de Andamento dos Projetos desenvolvidos na ISCMPA. Relatórios Parciais (pesquisas com duração superior à 6 meses), Relatórios Finais (ao término da pesquisa) e os Resultados Obtidos (cópia da publicação).

2 – Para o início do projeto de pesquisa, o investigador deverá apresentar a chefia do serviço (onde será realizada a pesquisa), o Parecer Consubstanciado de aprovação do protocolo pelo Comitê de Ética.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_832401.pdf	30/11/2016 10:06:10		Aceito
Outros	Uso_de_Dados_e_Materiais.JPG	30/11/2016 10:04:46	Pedro Dal Lago	Aceito
Outros	Termo_de_Compromisso_Relatorios_UFCSPA.JPG	30/11/2016 10:04:09	Pedro Dal Lago	Aceito
Outros	Formulario_de_inscricao.JPG	30/11/2016 10:03:20	Pedro Dal Lago	Aceito
Outros	Autorizacao_Chefia.JPG	30/11/2016 10:02:53	Pedro Dal Lago	Aceito
Outros	Confidencialidade.JPG	30/11/2016 10:02:27	Pedro Dal Lago	Aceito
Outros	Dados_de_Prontuario_e_Publicacao.JPG	30/11/2016 10:01:54	Pedro Dal Lago	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_de_Pesquisa.doc	30/11/2016 10:01:20	Pedro Dal Lago	Aceito
Orçamento	Orcamento.JPG	30/11/2016 10:00:21	Pedro Dal Lago	Aceito
Outros	Isencao_de_onus.JPG	30/11/2016 10:00:00	Pedro Dal Lago	Aceito
Cronograma	Cronograma.JPG	30/11/2016 09:53:20	Pedro Dal Lago	Aceito
Folha de Rosto	FolhaDeRosto.docx	30/11/2016 09:52:52	Pedro Dal Lago	Aceito

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Continuação do Parecer: 1.888.166

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

PORTO ALEGRE, 10 de Janeiro de 2017

Assinado por:
ELIZETE KEITEL
(Coordenador)

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7.2 Normas do Periódico

Journal of Cardiothoracic Surgery

Research article

Data sharing and availability

JCTS strongly encourages that all datasets on which the conclusions of the paper rely should be available to readers. We encourage authors to ensure that their datasets are either deposited in publicly available repositories (where available and appropriate) or presented in the main manuscript or additional supporting files whenever possible. Please see Springer Nature's information on recommended repositories.

Preparing your manuscript

The information below details the section headings that you should include in your manuscript and what information should be within each section.

Please note that your manuscript must include a 'Declarations' section including all of the subheadings (please see below for more information).

Title page

The title page should:

present a title that includes, if appropriate, the study design e.g.:

"A versus B in the treatment of C: a randomized controlled trial", "X is a risk factor for Y: a case control study", "What is the impact of factor X on subject Y: A systematic review"

or for non-clinical or non-research studies a description of what the article reports

list the full names, institutional addresses and email addresses for all authors

if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the "Acknowledgements" section in accordance with the instructions below

- Indicate the corresponding author

Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. Reports of randomized controlled trials should follow the CONSORT extension for abstracts. The abstract must include the following separate sections:

- **Background:** the context and purpose of the study
- **Methods:** how the study was performed and statistical tests used
- **Results:** the main findings
- **Conclusions:** brief summary and potential implications
- **Trial registration:** If your article reports the results of a health care intervention on human participants, it must be registered in an appropriate registry and the registration number and date of registration should be in stated in this section. If it was not registered prospectively (before enrollment of the first participant), you should include the words 'retrospectively registered'. See our editorial policies for more information on trial registration

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

Methods

The methods section should include:

- the aim, design and setting of the study
- the characteristics of participants or description of materials
- a clear description of all processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses

- the type of statistical analysis used, including a power calculation if appropriate

Results

This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

Discussion

This section should discuss the implications of the findings in context of existing research and highlight limitations of the study.

Conclusions

This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations should be provided.

Declarations

All manuscripts must contain the following sections under the heading 'Declarations':

- Ethics approval and consent to participate
- Consent for publication
- Availability of data and material
- Competing interests
- Funding
- Authors' contributions
- Acknowledgements
- Authors' information (optional)

Please see below for details on the information to be included in these sections.

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Ethics approval and consent to participate

Manuscripts reporting studies involving human participants, human data or human tissue must:

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- include the name of the ethics committee that approved the study and the committee's reference number if appropriate

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If your manuscript does not report on or involve the use of any animal or human data or tissue, please state "Not applicable" in this section.

Consent for publication

If your manuscript contains any individual person's data in any form (including any individual details, images or videos), consent for publication must be obtained from that person, or in the case of children, their parent or legal guardian. All presentations of case reports must have consent for publication.

You can use your institutional consent form or our consent form if you prefer. You should not send the form to us on submission, but we may request to see a copy at any stage (including after publication).

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If your manuscript does not contain data from any individual person, please state "Not applicable" in this section.

Availability of data and materials

All manuscripts must include an 'Availability of data and materials' statement. Data availability statements should include information on where data supporting the results reported in the article can be found including, where applicable, hyperlinks to publicly archived datasets analysed or generated during the study. By data we mean the minimal dataset that would be necessary to interpret, replicate and build upon the findings reported in the article. We recognise it is not always possible to share research data publicly, for instance when individual privacy could be compromised,

and in such instances data availability should still be stated in the manuscript along with any conditions for access.

Data availability statements can take one of the following forms (or a combination of more than one if required for multiple datasets):

- The datasets generated and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS]
- The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
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All financial and non-financial competing interests must be declared in this section.

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Acknowledgements

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Endnotes should be designated within the text using a superscript lowercase letter and all notes (along with their corresponding letter) should be included in the Endnotes section. Please format this section in a paragraph rather than a list.

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Example reference style:

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Smith JJ. The world of science. *Am J Sci*. 1999;36:234-5.

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Rohrmann S, Overvad K, Bueno-de-Mesquita HB, Jakobsen MU, Egeberg R, Tjønneland A, et al. Meat consumption and mortality - results from the European Prospective Investigation into Cancer and Nutrition. *BMC Medicine*. 2013;11:63.

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OnlineFirst chapter in a series (without a volume designation but with a DOI)

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Complete book, authored

Blenkinsopp A, Paxton P. Symptoms in the pharmacy: a guide to the management of common illness. 3rd ed. Oxford: Blackwell Science; 1998.

Online document

Doe J. Title of subordinate document. In: The dictionary of substances and their effects. Royal Society of Chemistry. 1999. [http://www.rsc.org/dose/title of subordinate document](http://www.rsc.org/dose/title%20of%20subordinate%20document). Accessed 15 Jan 1999.

Online database

Healthwise Knowledgebase. US Pharmacopeia, Rockville. 1998. <http://www.healthwise.org>. Accessed 21 Sept 1998.

Supplementary material/private homepage

Doe J. Title of supplementary material. 2000. <http://www.privatehomepage.com>. Accessed 22 Feb 2000.

University site

Doe, J: Title of preprint. <http://www.uni-heidelberg.de/mydata.html> (1999). Accessed 25 Dec 1999.

FTP site

Doe, J: Trivial HTTP, RFC2169. <ftp://ftp.isi.edu/in-notes/rfc2169.txt> (1999). Accessed 12 Nov 1999.

Organization site

ISSN International Centre: The ISSN register. <http://www.issn.org> (2006). Accessed 20 Feb 2007.

Dataset with persistent identifier

Zheng L-Y, Guo X-S, He B, Sun L-J, Peng Y, Dong S-S, et al. Genome data from sweet and grain sorghum (*Sorghum bicolor*). GigaScience Database. 2011. <http://dx.doi.org/10.5524/100012>.

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