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Avaliação de parâmetros hematológicos na predição de eventos cardiovasculares adversos em pacientes com infarto agudo do miocárdio submetidos à intervenção coronariana percutânea primária

Tese de Doutorado

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Programa de Pós-Graduação em Ciências da Saúde:

Cardiologia e Ciências Cardiovasculares

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"A simplicidade é o último grau de sofisticação"

(Leonardo DaVinci)

SUMÁRIO

LISTA DE ABREVIATURAS E SIGLAS

Língua Portuguesa

AVE: Acidente vascular encefálico

CRM: Cirurgia de revascularização do miocárdio

DAC: Doença arterial coronariana

ECAM: Eventos cardiovasculares adversos maiores

ECG: Eletrocardiograma em repouso

IAM: Infarto agudo do miocárdio

IAMCSST: Infarto agudo do miocárdio com supradesnivelamento do segmento ST

IC 95%: Intervalo de confiança de 95%

ICP: Intervenção coronariana percutânea

IH: Intra-hospitalar

NLR: Razão entre neutrófilos e linfócitos

RR: Risco relativo

VPM: Volume plaquetário médio

Língua Inglesa

ROC: *Receiver operating characteristic*

AUC: *Area under the curve*

MPV: *Mean platelet volume*

NLR: *Neutrophil-to-lymphocyte ratio*

STEMI: *ST segment elevation myocardial infarction*

MACE: *Major adverse cardiovascular events*

PCI: *Percutaneous coronary intervention*

RDW: *Red cell distribution width*

RR: *Relative risk*

95% CI: 95% *confidence interval*

RESUMO

O objetivo do presente trabalho foi investigar o papel de parâmetros hematológicos, como volume plaquetário médio (VPM), razão de neutrófilos e linfócitos (NLR) e *red cell distribution width* (RDW), na predição de eventos adversos, em pacientes com infarto agudo do miocárdio com supradesnivelamento do segmento ST submetidos à intervenção coronariana percutânea primária. Este foi um estudo de coorte prospectivo realizado em hospital terciário. Foi feita análise da curva ROC (*Receiver operating characteristic curve*) para calcular a área sob a curva (AUC – *area under the curve*) para a ocorrência de mortalidade e de eventos cardiovasculares adversos maiores (MACE – *major adverse cardiovascular events*) em curto e longo prazo. Na análise multivariada, o RDW permaneceu preditor independente de mortalidade e MACE a longo prazo [risco relativo (RR)=1,51; p=0,007 e RR=1,42; p=0,004]. As AUC para mortalidade e MACE foram de 0,65 (p<0,0001) e 0,62 (p<0,0001), respectivamente. Em relação ao NLR, permaneceu como preditor independente de MACE intra-hospitalar (RR=1,01; p=0,02), com AUC de 0,57 (p=0,03). O VPM não se manteve como preditor dos desfechos avaliados. Em conclusão, RDW elevado foi preditor independente de mortalidade e MACE a longo prazo. NLR elevada foi preditor independente de MACE intra-hospitalar. Na prática clínica, o hemograma completo, incluindo a contagem de leucócitos, é realizada rotineiramente durante a hospitalização. Por serem altamente disponíveis na pratica clínica, com custo acessível e práticos, esses parâmetros podem ser mais uma ferramenta a ser utilizada à beira do leito.

Palavras-chave: Infarto Agudo do Miocárdio; Angioplastia; Mortalidade; Inflamação.

ABSTRACT

The aim of the present study was to investigate the role of hematological parameters, such as mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR) and red cell distribution width (RDW), in the prediction of adverse events in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. This was a prospective cohort study conducted at a tertiary hospital. Analysis of the ROC curve (receiver operating characteristic curve) was performed to calculate the area under the curve (AUC) for the occurrence of mortality and major adverse cardiovascular events (MACE) in short and long term. In multivariate analysis, RDW remained an independent predictor of mortality and long-term MACE [relative risk (RR) = 1.51; p = 0.007 and RR = 1.42; p = 0.004]. The AUC mortality and MACE were 0.65 (p <0.0001) and 0.62 (p <0.0001), respectively. Regarding NLR, it remained as an independent predictor of in-hospital MACE (RR = 1.01; p = 0.02), with an AUC of 0.57 (p = 0.03). MPV was not maintained as an independent predictor of the assessed outcomes. In conclusion, elevated RDW was an independent predictor of all-cause mortality and long-term MACE. Elevated NLR was an independent predictor of in-hospital MACE. In the clinical practice, a complete blood count, including white blood cell count, is routinely performed during hospitalization. Because they are highly available in clinical practice, affordable and practical, these parameters can be another tool to be used at the bedside.

Keywords: Acute Myocardial Infarction; Angioplasty; Mortality; Inflammation.

1. INTRODUÇÃO

De acordo com a Organização Mundial da Saúde, aproximadamente, 17,9 milhões de pessoas morrem anualmente devido a doenças cardiovasculares. Dessas, 80% são relacionadas a acidente vascular encefálico ou infarto agudo do miocárdio (IAM)[1]. Dessa forma, a doença arterial coronariana permanece como uma das maiores causas de morte ao redor do mundo[2]. Dentre seu espectro clínico, o infarto agudo do miocárdio apresenta uma alta mortalidade apesar dos avanços terapêuticos nas últimas décadas. No Brasil, foram registradas 95.557 mortes em 2019 por IAM, sendo 5.191 mortes apenas no Rio Grande do Sul[3].

A doença arterial coronariana, usualmente, decorre de um processo de obstrução das coronárias devido à formação da placa ateromatosa. A sua patogênese envolve um desequilíbrio no mecanismo lipídico e uma resposta imune inadequada, levando à inflamação crônica da parede de artérias[4].

Quando a placa atinge um grau de estenose maior que 50% do diâmetro do vaso, levando à uma restrição do fluxo sanguíneo, pode ocorrer um desequilíbrio na oferta e demanda de oxigênio. Nos momentos em que a demanda se encontra elevada, como no exercício físico, esse processo pode levar à hipóxia e causar o sintoma de angina[5].

O infarto agudo do miocárdio ocorre quando há necrose miocárdica. Na prática, ele pode ser diagnosticado com base na apresentação clínica, eletrocardiograma (ECG), exames laboratoriais e exames de imagens invasivos

e não invasivos. Inicialmente, o infarto agudo do miocárdio pode ser classificado de acordo com a presença ou ausência da elevação do segmento ST – que corresponde à presença ou não de necrose transmural da parede[6]. Contudo, ainda pode ser classificado em 6 tipos de infarto. 1) complicação ateroesclerótica; 2) desbalanço na oferta-demanda na ausência de complicação aguda aterosclerótica; 3) morte súbita sem confirmação de biomarcador ou por ECG; 4a) relacionado à intervenção percutânea coronariana (ICP); 4b) relacionado à trombose de stent; 5) relacionado à cirurgia de revascularização do miocárdio (CRM)[7].

A ruptura ou erosão da placa aterosclerótica, resultando na exposição do matéria trombogênico ao sangue circulante, é o mecanismo mais frequente pelo qual o IAM ocorre[8]. Quando a oclusão é completa, usualmente, temos o IAM com supradesnivelamento do segmento ST (IAMCSST).

Sabe-se que o tratamento efetivo e precoce do IAM - através da instituição de terapia de reperfusão - é o componente mais importante do tratamento. A reperfusão coronariana pode ser obtida por meio da terapia fibrinolítica ou da ICP. A superioridade de cada terapia depende das condições clínicas e anatômicas de cada paciente. As diretrizes atuais recomendam que a ICP aconteça em um tempo ≤90 minutos do primeiro contato médico ou dentro de 12 horas dos sintomas[9]. Este processo é crucial para o seu desfecho clínico, com redução do tamanho do infarto, preservação da função ventricular e diminuição importante de morbimortalidade, sendo que o benefício de qualquer tipo de tratamento diminui na medida em que aumenta o tempo do início dos sintomas[10].

De forma geral, a angioplastia reduz a área estenótica e aumenta a área luminal do vaso, com o objetivo de restabelecer o fluxo. Isso pode ocorrer tanto pela aspiração do trombo, pela inflação de um balão ou pela introdução de um stent. É importante ressaltar que 95% dos pacientes atingem a reperfusão coronariana completa quando são submetidos à ICP, enquanto apenas 50-60% dos pacientes atingem a reperfusão completa quando recebem a terapia fibrinolítica. Em uma meta-análise realizada em 2003, com 23 estudos, que comparou 3.872 pacientes submetidos à ICP, com 3.867 pacientes submetidos à terapia fibrinolítica, e que analisou a mortalidade em 30 dias, se verificou que os pacientes submetidos à angioplastia apresentaram menor taxa de mortalidade, menor taxa de reinfarto, e menos acidente vascular encefálico (AVE)[11].

Contudo, apesar da superioridade da angioplastia nesse cenário, ela não é isenta de riscos, seja pela condição inerente do paciente, seja pelo procedimento, e essas complicações interferem diretamente no custo assistencial dos pacientes. Um estudo realizado na *Mayo Clinic*[12] entre 1998 e 2003 estimou um custo aproximado de U$S 9.000,00 acima para cada paciente que apresentasse algum evento cardiovascular adverso, comparado com os pacientes sem complicação. Portanto, apesar de eventos cardiovasculares adversos maiores terem ocorrido em apenas 13% dos pacientes, isso correspondeu a 25% dos gastos com hospitalização para os pacientes submetidos à ICP primária. Apesar de o cuidado dos pacientes infartados ter melhorado substancialmente nas últimas décadas e as fatalidades envolvendo esta condição terem reduzido, a busca por melhorias permanece. Portanto, a

busca de novas ferramentas para identificar pacientes de maior risco de desenvolver complicações é necessária.

2. REVISÃO DA LITERATURA

2.1 Biomarcadores e marcadores inflamatórios

Biomarcadores representam determinada mudança bioquímica em um nível orgânico ou tissular associado com processos biológicos ou patológicos[13]. A definição, padronizada em 2001, considera como uma característica que é mensurada objetivamente e avaliada como indicador de processos biológicos normais, patogênicos ou como resposta a uma intervenção terapêutica. Eles podem ser obtidos de uma amostra biológica - urina, sangue ou outro tecido –, ou de um dado de uma pessoa (pressão arterial, ECG), ou ser um teste de imagem (ecocardiograma, tomografia computadorizada)[14].

Podem ser classificados de diversas formas, como biomarcadores antecedentes (para avaliar o risco de desenvolver uma doença de interesse); de rastreamento (para detectar alguma doença subclínica); diagnósticos; de estadiamento (para caracterizar a severidade de uma doença); e prognósticos (para predizer o curso clínico, incluindo recorrência, resposta à terapia e para monitorizar o efeito da terapia)[14].

Independente do propósito do seu uso, um novo biomarcador será clinicamente útil se for acurado, reproduzível, aceitável pelo paciente e de fácil interpretação pelos médicos, além de apresentar sensibilidade e especificidade adequadas para o desfecho no qual é esperado identificar. Portanto, definir valores anormais é um passo crítico antes do uso ser difundido na pratica clínica.

É fundamental caracterizar a distribuição na população e em amostras de pacientes nas quais os biomarcadores serão utilizados[14]. O IAM é causado por uma ruptura da placa aterosclerótica em grande parte dos casos. Desde que a aterosclerose é considerada uma doença inflamatória, alguns marcadores inflamatórios foram propostos para avaliar o risco cardiovascular.

2.2 Volume Plaquetário Médio

As plaquetas desempenham um papel importante na fisiopatologia da doença arterial coronariana (DAC)[15]. Atualmente, admite-se que o tamanho das plaquetas seja um indicador sensível de sua reatividade e que sua magnitude é determinante na formação do trombo intracoronariano em presença de ruptura da placa aterosclerótica[16]. Plaquetas jovens são maiores e mais reativas, e, portanto, podem levar à maior adesão e agregação plaquetárias e resultar em eventos tromboembólicos[17]. O volume plaquetário médio (VPM) está aumentado em pacientes com IAM, se comparado com pacientes com angina estável[18], e tem sido utilizado como marcador de eventos após infarto agudo do miocárdio.

O aumento do tamanho de plaquetas também está ligado a outros marcadores de atividade, incluindo agregação plaquetária, síntese aumentada de tromboxana, liberação de b-tromboglobulina e expressão aumentada de moléculas de adesão[19]. Além disso, existe uma interação entre plaquetas e neutrófilos que leva a uma agregação aumentada de plaquetas, obstruindo capilares e bloqueando o fluxo mecanicamente. Finalmente, células endoteliais danificadas, neutrófilos e plaquetas contribuem para uma vasoconstrição sustentada da microcirculação coronária via liberação de vasoconstritores.

Diversas outras situações, como diabetes, hipertensão, tabagismo, obesidade e inflamação, estão associadas com valores elevados de VPM[20–23]. Logicamente, é possível que o volume plaquetário médio esteja alterado na DAC devido à presença desses fatores de risco. No entanto, estudos evidenciaram que o VPM era um fator de risco independente após ajustar para estes fatores[24–26].

Gonçalves et al. (2011) [27] analisaram a utilidade do VPM como biomarcador de prognóstico após intervenção coronariana percutânea. Os níveis de troponina T e VPM elevados foram preditores de morte e infarto agudo do miocárdio a longo prazo. Em outro estudo, realizado com 1.082 pacientes com IAM, percebeu-se que os pacientes que possuíam um VPM >9 fL apresentaram maiores taxas de mortalidade, insuficiência cardíaca e episódios de angina pós-infarto durante a internação[28].

2.3 Razão de Neutrófilos e Linfócitos

Alguns estudos já documentaram a relação entre elevação da contagem total de leucócitos circulantes com o aumento do risco cardiovascular[29–31]. Os leucócitos têm papel importante na progressão da doença coronariana, na desestabilização e na ruptura da placa aterosclerótica, levando a eventos trombóticos[32–34]. Estudos prévios em modelos animais demonstraram um tropismo dos leucócitos por tecidos inflamados, ocorrendo, assim, uma invasão na placa, tornando-a mais vulnerável à ruptura pela liberação de enzimas proteolíticas e derivados do ácido araquidônico[35].

Em condições como diabetes mellitus tipo 2, dislipidemia, doença renal crônica, obesidade e apneia obstrutiva do sono, leucócitos liberam mediadores inflamatórios em uma taxa mais rápida quando comparado com indivíduos hígidos[30]. Essas interações contínuas das células inflamatórias com as células endoteliais podem causar mínimas lesões crônicas ao endotélio, representando um *link* entre a ativação dos neutrófilos e a patogênese da aterosclerose[36]. Vale ressaltar que a isquemia miocárdica por si só é um estímulo para a ativação e migração neutrocitária para a zona infartada; os neutrófilos são uma das primeiras células inflamatórias recrutadas para os tecidos durante a inflamação[37].

Obtida através da divisão da contagem total de neutrófilos pela contagem total de linfócitos, a razão entre neutrófilos e linfócitos (NLR) surgiu como potencial marcador inflamatório, que vem sendo associado com piores desfechos cardiovasculares em pacientes com síndrome coronariana aguda. Os dados referentes à população saudável não foram muito bem elucidados; contudo, Forget e colaboradores encontraram valores de NLR entre 0,78 e 3,53 em adultos saudáveis[38]. Horne *et al.* (2005)[39] observaram a significância da NLR com DAC em uma coorte com mais de 3.000 pacientes com angina estável, em que pacientes com NLR acima de 4,1 tiveram risco aumentado para morte ou IAM durante o período de seguimento. Outro estudo, realizado por Hartaighr et al. (2012)[33], avaliou por 7,8 anos 3.316 pacientes com angina estável e instável, e encontrou dados que corroboram a NLR como preditor independente de mortalidade cardiovascular, mesmo após ajustado para infecção vigente. Ademais, observou-se que, conforme aumentava o quartil de NLR, maior era a incidência de eventos adversos ocorridos.

No contexto de doença cardíaca, uma contagem elevada de neutrófilos com menor contagem de linfócitos tem sido associada com infartos maiores, maiores taxas de insuficiência cardíaca após infarto agudo do miocárdio e pior sobrevida em indivíduos submetidos à intervenção coronariana percutânea, além de pior perfusão miocárdica[40–46]. Recentemente, Kim e colaboradores[47] observaram que a NLR aumenta ao longo do tempo em inidvíduos com DAC, atingindo valores elevados próximo ao momento do evento adverso. Portanto, esse índice elevado não apenas serve como um espelho da condição inflamatória exacerbada, mas, também, demonstra o papel dos neutrófilos na instabilidade da placa aterosclerótica. Isso pode ser explicado porque os neutrófilos são os primeiros leucócitos a infiltrarem no miocárdio infartado, liberando diversas enzimas proteolíticas que causam ruptura da placa, ativação da cascata de coagulação e instabilidade elétrica cardíaca[48–50]. Ademais, há evidência de que a vida útil dos neutrófilos se prolongue em placas instáveis[51]. Ao contrário dos neutrófilos, os linfócitos diminuem devido ao aumento dos níveis de cortisol, catecolaminas e citocinas pró-inflamatórias no IAMCSST[52,53]. Vale ressaltar, também, que existe agregação entre plaquetas e neutrófilos que preenche os capilares, bloqueando o fluxo mecanicamente. Por fim, o dano endotelial, os neutrófilos e as plaquetas contribuem para uma vasoconstrição sustentada da microcirculação através da liberação de substâncias vasoconstritoras. Isso sugere que uma resposta inflamatória sustentada define piores desfechos para esses pacientes.

2.4 Red cell distribution width

Dados a respeito do RDW no cenário do infarto são limitados na literatura. Entretanto, um valor de, pelo menos, 13,6% é considerado elevado[54]. Um valor elevado de RDW tem sido demonstrado como preditor independente de eventos adversos cardiovasculares após IAMCSST[55–59]. Contudo, dados acerca da sua capacidade prognóstica são limitados. Isik et al[59] encontraram uma área sob a curva para mortalidade de 0,83 com um valor de RDW de 13,8% (sensibilidade de 80%; especificidade de 64%) nos pacientes com IAMCSST submetidos à ICP.

O mecanismo pelo qual o RDW é associado com piores desfechos não é completamente elucidado. A principal hipótese decorre da consequência do estresse inflamatório, levando a uma produção inadequada de eritrócitos e ativação plaquetária[60]. Esses achados são suportados por Lippi e colaboradores[61], os quais observaram uma correlação positiva entre o aumento do RDW, o aumento dos valores de proteina C reativa e a velocidade de hemossedimentação. Além disso, citocinas pró-inflamatórias, como TNF-α, IL-1 e IL-6, inibem a maturação de eritrócitos na medula óssea, fazendo com que sejam liberadas formas imaturas na corrente sanguínea.

Ferrario e colaboradores[62] observaram que os níveis plasmáticos de eritropoietina aumentam nos pacientes com IAMCSST e persistem elevados até sete dias após o evento, quando comparado com controles. O fato de a trombopoietina e a eritropoeitina terem estruturas consideravelmente similares pode levar a um aumento na reatividade plaquetária[63], e é outra evidência que suporta a associação entre RDW e inflamação.

Medidas alteradas de RDW podem estar relacionadas à anemia ferropriva, associada a pior prognóstico em pacientes com doença arterial coronariana estável e instável[64,65]. Pacientes com anemia têm dano isquêmico do miocárdio devido à diminuição do conteúdo de oxigênio suprindo o miocárdio[66], um débito cardíaco maior para manter o fornecimento sistêmico adequado de oxigênio[67] e comprometimento da microcirculação coronariana[68]. Além disso, a anemia está associada à doença renal e a outros distúrbios crônicos/inflamatórios que podem contribuir para uma sobrevida diminuída.

3. JUSTIFICATIVA E OBJETIVOS

3.1 Justificativa

Marcadores inflamatórios têm sido utilizados para estratificação de risco de pacientes para eventos adversos. Um marcador necessita ser acurado, prático, disponível na prática clínica e com custo acessível. Quando existe mais de uma ferramenta disponível, precisamos avaliar qual é a melhor e mais acurada. Como o hemograma é um exame de rotina e apresenta baixo custo, a relação entre neutrófilos e linfócitos, volume plaquetário médio e RDW podem ser marcadores custo-efetivos e possíveis indicadores de risco cardiovascular.

3.2 Objetivo primário

- Avaliar o desempenho da NLR, VPM e RDW na predição de eventos cardiovasculares adversos em pacientes com IAMCSST submetidos à ICP primária.

3.3 Objetivos secundários

- Avaliar a associação independente da NLR, VPM e RDW com:
    1. mortalidade a curto e longo prazo.
    2. eventos cardiovasculares adversos maiores (MACE) a curto e longo prazo.

- Estabelecer os valores preditivos, curva ROC e determinação da área sob a curva para analisar qual a precisão e acurácia na predição de eventos adversos.

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Comparison of neutrophil-to-lymphocyte ratio and mean platelet volume in the prediction of adverse events after primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction

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FIGURES: 2

TABLES: 2

KEYWORDS: Myocardial infarction; percutaneous coronary intervention; mortality, mean platelet volume, neutrophil-to-lymphocyte ratio

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ABSTRACT

BACKGROUND AND AIMS: Elevated neutrophil-to-lymphocyte ratio (NLR) and mean platelet volume (MPV) are indirect inflammatory markers. There is some evidence that both are associated with worse outcomes in ST-segment elevation myocardial infarction (STEMI) after primary percutaneous coronary intervention (PCI). The aim of the present study was to compare the capacity of NLR and MPV to predict adverse events after primary PCI.

METHODS: In a prospective cohort study, 625 consecutive patients with STEMI who underwent primary PCI were followed. Receiver operating characteristic (ROC) curve analysis was performed to calculate the area under the curve (AUC) for the occurrence of procedural complications, mortality and major adverse cardiovascular events (MACE).

RESULTS: Mean age was 60.7(±12.1) years, 67.5% were male. The median of NLR was 6.17(3.8-9.4) and MPV was 10.7(10.0-11.3). In multivariate analysis, both NLR and MPV remained independent predictors of no-reflow (relative risk [RR]=2.26; 95%confidence interval [95%CI]=1.16-4.32;*p*=0.01 and RR=2.68;95%CI=1.40-5.10;*p*<0.01, respectively), but only NLR remained an independent predictor of in-hospital MACE (RR=1.01;95%CI=1.00-1.06;*p*=0.02). The AUC for in-hospital MACE was 0.57 for NLR (95%CI=0.53-0.60;*p*=0.03) and 0.56 for MPV(95%CI=0.52–0.60;*p*=0.07). However, when AUC`s were compared with DeLong test, there was no statistically significant difference for these outcomes(*p*>0.05). NLR had an excellent negative predictive value(NPV) of 96.7 for no-reflow and 89.0 for in-hospital MACE.

CONCLUSIONS: Despite no difference in the ROC curve comparison with MPV, only NLR remained an independent predictor for in-hospital MACE. A low NLR has an

excellent NPV for no-reflow and in-hospital MACE what could be of clinical relevance in the management of low-risk patients.

1. INTRODUCTION

Acute myocardial infarction is caused by coronary plaque rupture in the vast majority of cases. Since atherosclerosis it is regarded as an inflammatory disease, some inflammatory markers have been proposed to evaluate cardiovascular risk (2). Leukocytes play a crucial role in the progression of atherosclerosis and in destabilization and rupture of a plaque, leading to thrombotic events(3). The neutrophil-to-lymphocyte ratio is obtained by dividing the total count of neutrophil by the total count of lymphocyte and has been shown to be associated with worse outcomes in patients with acute coronary syndromes and established coronary heart disease(4–8).

Likewise, platelets play an important role in the pathophysiology of coronary artery disease(9). Currently, it is assumed that platelet size is a sensitive indicator of its reactivity(10). Young platelets are larger and more reactive, which can lead to increased adhesion and platelet aggregation resulting in thromboembolic events(11). The mean platelet volume (MPV) is a marker of platelet activation and an elevated pre-procedural MPV is associated with increased mortality in ST-elevation acute myocardial infarction (STEMI) patients submitted to primary percutaneous coronary interventions (PCI) (12)

The aim of the present study was to compare NLR and MPV for the prediction of adverse events in patients presenting with STEMI submitted to primary PCI.

2. METHODS

2.1 Study protocol

This was a prospective single-center Cohort study. Data from medical records were transferred to standardized case report forms (CRFs). The following variables were collected: baseline clinical characteristics, medical history, procedure characteristics, reperfusion strategy, initial and final thrombolysis in myocardial

infarction (TIMI) flow grade, and discharge therapies. In-hospital and thirty-day mortality rates were also recorded in the CRF. Thirty-day and 1-year follow-up were ascertained by clinical visit and telephone contact.

Blood samples were collected by venipuncture before the procedure as part of routine patient care. Neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing neutrophil count from lymphocyte count, both obtained from the same blood sample drawn on admission. Mean platelet volume is automatically performed during platelet count. Blood parameters were analyzed by the XE 5000 (Sysmex®, Norderstedt, Germany). All patients were pre-treated with a loading dose of acetylsalicylic acid (300mg) and clopidogrel (600mg), and unfractionated heparin was used during procedure (70-100 UI/kg). Use of IIb/IIIa glycoprotein, aspiration thrombectomy and PCI technical strategies (i.e. pre-dilation, direct stent placement, post-dilation) were performed according to operator`s choice or at discretion of each operator. Coronary flow before and after the procedure was assessed and described according to the TIMI criteria. Anticoagulants were suspended after the end of procedure, and the dual antiplatelet therapy was recommended for 12 months after the event. Creatinine was measured at baseline and 48-72 hours post-procedure.

2.2 Research subjects

Consecutive patients with STEMI who underwent primary PCI in a tertiary, reference university hospital with 24-hour primary PCI availability in southern Brazil, between March 2011 and March 2018 were included. STEMI was defined as typical chest pain at rest associated with ST-segment elevation of at least 1 mm in two contiguous leads in the frontal plane or 2 mm in the horizontal plane, or typical pain at rest in patients with a new, or presumably new, left bundle-branch block. Exclusion

criteria were the lack of follow-up, laboratory tests were not collected before PCI or failure to perform PCI. This study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Institutional Research and Ethics Committee and written informed consent was obtained from all individual participants included in the study.

2.3 Clinical definitions

Major cardiovascular events (MACE) were defined as death from any cause, new myocardial infarction (MI), stent thrombosis and stroke after primary PCI. New MI was defined as recurrent chest pain with ST-segment elevation or new Q waves and raise of serum biomarkers after their initial decrease. Stroke was defined as a new, sudden-onset focal neurological deficit, of presumably cerebrovascular cause, irreversible (or resulting in Death) and not caused by other readily identifiable causes. Complications during procedure were defined as distal embolization, no reflow phenomenon, residual stenosis, perforation, death during primary PCI, branch occlusion, and contrast-induced nephropathy. Contrast-induced nephropathy was a raise of 0.3 mg/dL or 50% in post-procedure (24–72 h) creatinine compared to baseline, proposed by the Acute Kidney Injury Network (AKIN) as a standardized definition of acute kidney injury.

2.4 Statistical Analysis

Continuous variables were expressed as mean (± standard deviation) or median (interquartile range [IQR]). Categorical variables were represented by their relative and absolute frequencies. Patients were separated into tertiles on the basis of serum of NLR and MPV on admission and the hypothesis that patients with the highest values would

have a greater event rate than those in the other tertiles was tested using a chi-square test. Correlations between the levels of MPV and NLR were analyzed by Spearman's rank correlation test. Receiver-operating characteristic (ROC) curves were used to evaluate the discriminatory power of the different scores. Youden index analysis was performed to determine the best cutoff value for predicting clinical endpoints. Multivariate analysis was performed by Poisson robust regression in order to evaluate the independent predictive value of NLR and MPV. P value was considered significant at ≤0.05. AUCs were compared with the De Long test, using MedCalc Statistical Software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium). All remaining statistical analyses were conducted using IBM SPSS Statistics, version 21.

3. RESULTS

Between March 2011 and March 2018, 714 consecutive patients presenting with STEMI were enrolled in our registry. Eighty-nine subjects were excluded because blood tests were not collected before PCI or because PCI was not performed. Therefore, 625 patients were included in the final analysis. Patients were divided in tertiles according to their NLR and MPV values. Elevated value was defined as those in the upper tertile or ≥ 9.41 for NLR and ≥ 11.3 for MPV. Overall, mean age was 60.72(±12.14); 67.5% were male; 59% had hypertension; 23.7% had diabetes and NLR and MPV median value was 6.17(3.84- 9.41) and 10.7 (10-11.3) respectively. Thirty-day MACE occurred in 16.7% of patients; death occurred in 8.6% during hos7pitalization and in 13.5% of the cases at 1 year. Baseline characteristics and adverse outcomes are shown in **Table 1.** There were more patients with Killip III/IV (22.4% vs. 16.4%) in the high NLR group when compared to the high MPV group.

In univariate analysis, patients with higher values of NLR had a significantly greater risk of no-reflow, distal embolization, CIN, procedural complications, in-hospital death, and in-hospital MACE without a significant increase in the risk of short-term MACE, and 1-year all-cause mortality. Patients with higher values of MPV had a significantly greater risk of no-reflow, procedure complication, in-hospital MACE. In multivariate analysis, when adjusted by age, pain-to-door time, creatinine pre-procedure, TIMI score, left ventricle ejection fraction < 35 before discharge, number of vessels, only NLR remained an independent predictor of in-hospital MACE (relative risk [RR] = 1.01 95% confidence interval [95%CI] = 1.00-1.06; p = 0.02). When adjusted by drug-eluting stent (DES), TIMI flow 2 or 3 after procedure, abciximab use, age, total length of stents both NLR and MPV remained independent predictors of no-reflow (RR = 2.26; 95%CI = 1.16-4.32; p = 0.01 and RR = 2.68; 95%CI = 1.40-5.10; p < 0.01, respectively) **(Table 2).**

There was no correlation between MPV and NLR (r = 0.007, p=0.86) (**Figure 1**). **Figure 2** presents the ROC curves. Area under the ROC curve of NLR for in-hospital MACE, no-reflow and procedure complication were 0.57 (95%CI = 0.53-0.60; p=0.03), 0.64 (95%CI = 0.60-0.68; p=0.0002), 0.62 (95%CI = 0.58-0.66; p <0.0001) respectively and for MPV were 0.56 (95%CI = 0.52 – 0.60; p = 0.07) 0.62 (95%CI = 0.58-0.66; p = 0.005) 0.57 (95%CI = 0.53-0.61; p = 0.01). When AUC`s were compared two-by-two with DeLong test, there was no statistically significant difference for these outcomes (p > 0.05)Descriptive values of the prognostic accuracy of the test are described at **Figure 2** with Younden Index for the best cutoff point, sensibility, specificity and predictive values.

4. DISCUSSION

In our cohort of STEMI patients undergoing primary PCI, we found that NLR and MPV, obtained from routine admission blood count, are excellent tools to identify patients at high risk for developing peri-procedural complications and, as previously described in the literature, patients with higher values of NLR also had an increased risk of developing in-hospital MACE. To the best of our knowledge, this is the first study to determine the comparative value of these parameters.

Atherosclerosis is regarded as an inflammatory disease where leucocytes and platelets reactivity might have a central role. Data regarding NLR values in a healthy population are scarce. Forget et al(13) have studied 413 healthy individuals to determine a normal cut-off value, with values ranging from 0.78 to 3.53. Our patients were older, with multiple comorbidities and facing a life-threatening situation, therefore presenting higher values of NLR. Likewise, MPV, reflecting platelet activity, seems to be related to coronary artery disease (CAD) through association with multiples risk factors, such as diabetes, smoking, hypertension, obesity and inflammation(14–17).

Li et al observed that NLR was significantly higher in patients with thrombus formation in the infarct-related artery, which was the only predictor of no-reflow/slow flow during PCI.(18) This may explain the higher occurrence of no-reflow in patients with elevated values of NLR. Previous studies have shown a direct visualization of neutrophilic invasion of atherosclerotic plaque and their tropism for inflamed tissues, facilitating plaque rupture through the release of proteolytic enzymes, arachidonic acid derivatives, and superoxide radicals.(19,20) Therefore, the higher neutrophil count may not only mirror the exacerbated inflammatory condition found in patients with atherosclerotic disease but also may be associated with the role of those cells in the instability of atherosclerotic plaque.

It is known that platelets play an important role in the progression of atherosclerotic lesions, plaque destabilization, and thrombosis(10,11). Larger platelets are more active and exhibit an enhanced pro-thrombotic activity(21). Increased platelet size is also linked to other markers of activity, including platelet aggregation, enhanced thromboxane synthesis and β-thromboglobulin release, and increased expression of adhesion molecules(22). Consequently, this might explain our findings as MPV as a possible predictor of no-reflow. Moreover, there is an interaction between platelets and neutrophils that leads to enhanced platelet aggregation plugging capillaries and blocking flow mechanically. Finally, damaged endothelial cells, neutrophils and platelets contribute to a sustained vasoconstriction of coronary microcirculation via vasoconstrictors release.

The prognostic value of NLR and MPV for cardiovascular outcomes varies in the literature. For predicting in-hospital mortality, Pan et al (23) have found an area under the curve (AUC) for NLR of 0.607 (sensitivity: 63.7%, specificity: 61.1%) in patients with STEMI submitted to primary PCI. In a long-term analysis in the same population, Sen et al (6) have found that NLR at admission was a strong predictor of mortality within 3 years with an AUC of 0.79. Park and colleagues found similar results with an AUC of 0.72 and sensitivity, specificity, positive predictive value and negative predictive value of 72%, 68%, 16%, 97%, respectively.

Regarding MPV, Gonçalves et al (21) identified an AUC for MPV of 0.637 for death or new MI in 1-year for patients with STEMI submitted to primary PCI. In other long-term analysis in the same population, Navarta et al (24) found that MPV at admission was a strong predictor of mortality within 1 years with an AUC of 0.72. Moon and colleagues(25) found similar results with an AUC of 0.71 and a sensitivity and specificity of 87.5%, 45.1%, respectively. Our findings do not support the evidence

of long-term prognosis of these biomarkers, however, we demonstrated a moderate association of MPV and NLR with acute outcomes such as in-hospital mortality and no-reflow. When the AUC of MPV and NLR were compared for different outcomes, we did not observe any statistical difference, although only NLR remained an independent predictor of in-hospital MACE, possibly making NLR a more reliable test. Despite a low positive predictive value, NLR had an excellent negative predictive value, what might be of clinical relevance in the decision-making process of identifying high-risk STEMI patients undergoing primary PCI.

In our analysis, some strengths and limitations deserve to be highlighted. This study has limitations that are inherent in observational studies. Some data were obtained retrospectively, which can determine less reliable information. However, this study is a record of consecutive and unselected patients coming from a tertiary referral hospital in the treatment of acute coronary syndromes, so the data shown are highly applicable in daily clinical practice.

In conclusion, high NLR and MPV were independent predictors of no-reflow and NLR was also an independent predictor of in-hospital MACE in patients with STEMI submitted to primary PCI. A low NLR value has an excellent negative predictive value for these outcomes. Much remains to be learned about these biomarkers. It is essential to explore whether therapeutic adjustment of their levels could result in improvements of cardiovascular care. Although both NLR and MPV are simple, inexpensive, and widely available and do not require a specialist for interpretation, NRL only seems to be a more reliable tool to be used at bedside.

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AUTOR CONTRIBUTIONS:

Conceptualization: Machado GP, Valle FH, Wainstein R, Bergoli, LCC. **Data curation:** Carpes CK, Lech M, Mariani S. **Formal analysis:** Machado, GP, Neves GP. **Writing:** Machado GP, Araujo GN. **Supervision:** Gonçalves SC, Wainstein MV.

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Figure 1 Spearman correlation's between neutrophil–to–lymphocyte ratio (NLR) and mean platelet volume (MPV). Spearman's Coefficient = 0.012 *p*= 0.76.

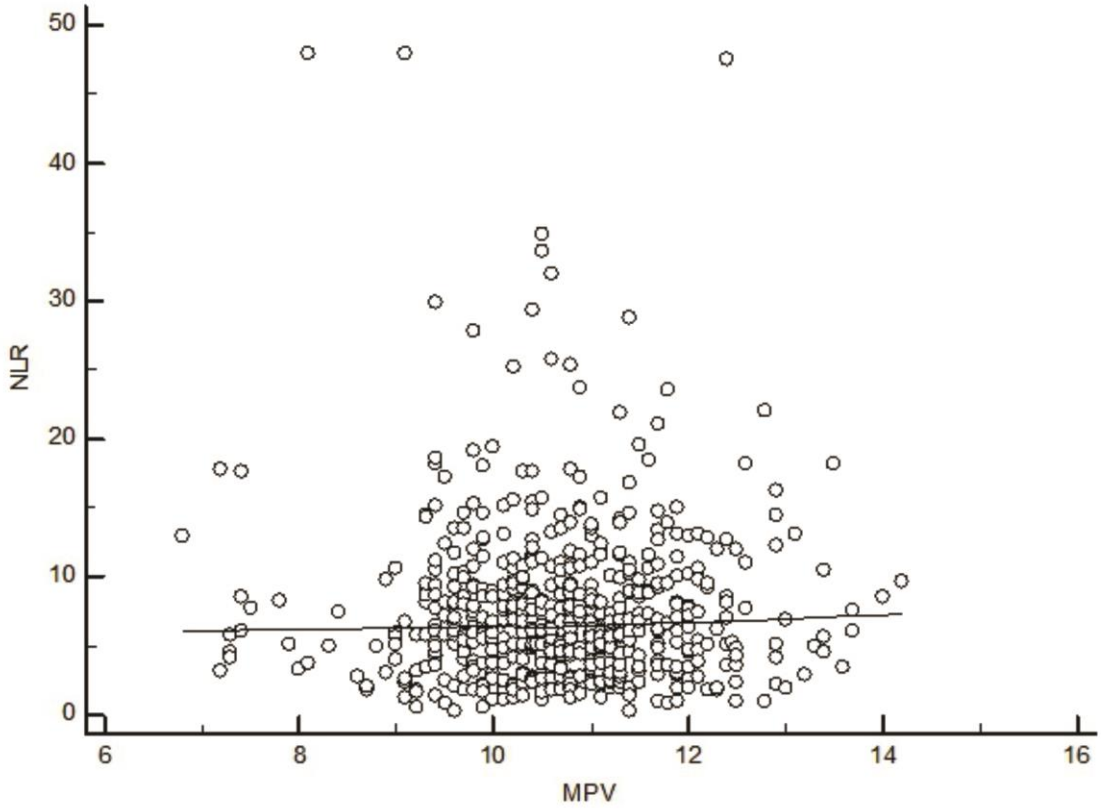
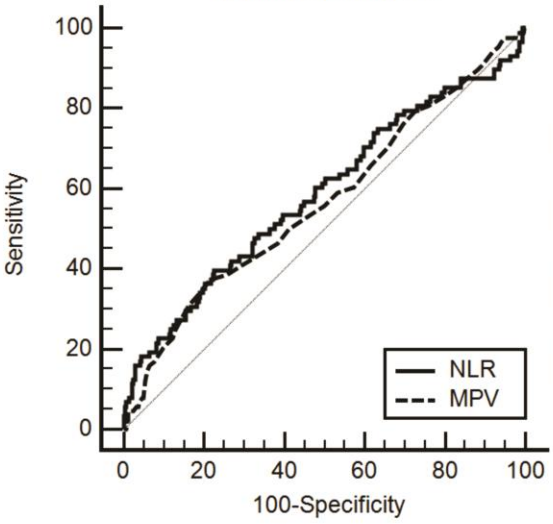


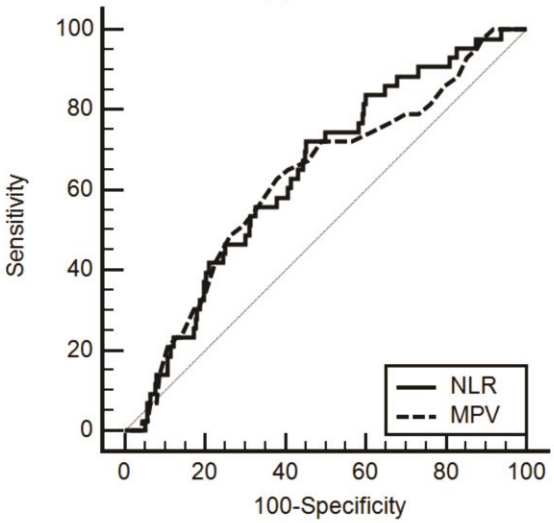
Figure 2 – Receiver operator characteristic (ROC) graphic showing areas under the curve (AUC) of neutrophil–to–lymphocyte ratio (NLR) and mean platelet volume (MPV) for (A) in-hospital major cardiovascular outcomes (MACE), (B) no–reflow and (C) procedural complications

(A) In-hospital MACE



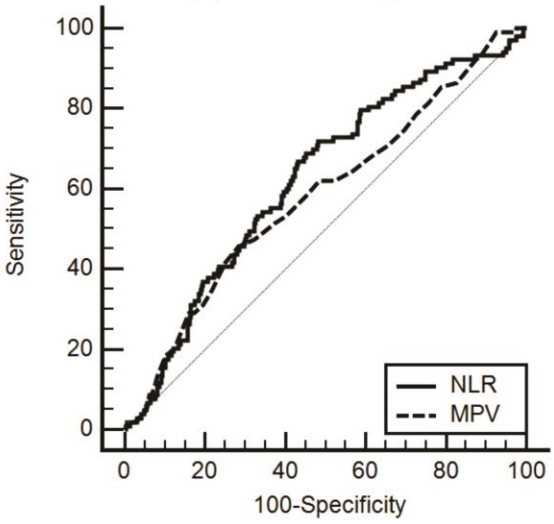
	NLR	MPV
Youden Index	>9.35	>11.3
AUC (95% CI)	0.57 (0.53 - 0.60)	0.56 (0.52 – 0.60)
Sensitivity	38.0 %	37.0%
Specificity	77.0 %	78.15%
PPV (95% CI)	30.5 (24.8 – 36.8)	20.9 (14.8 – 28.1)
NPV (95% CI)	87.4 (82.6 – 91.3)	88.9 (85.8 – 91.5)
p-value	0.68	

(B) No-reflow



	NLR	MPV
Youden Index	>6.59	>10.9
AUC (95% CI)	0.64 (0.60 - 0.68)	0.62 (0.58 – 0.66)
Sensitivity	73.3 %	62.7%
Specificity	55.4 %	51.7%
PPV (95% CI)	10.3 (7.2 – 14.2)	10.3 (6.9 – 14.7)
NPV (95% CI)	96.7 (94.4 – 98.3)	95.9 (93.5 – 97.7)
p-value	0.76	

(C) Procedure complication



	NLR	MPV
Youden Index	>6.59	>11.3
AUC (95% CI)	0.62 (0.58 - 0.66)	0.5 (0.53 – 0.61)
Sensitivity	67.6 %	45.3%
Specificity	57.3 %	71.4%
PPV (95% CI)	22.3 (17.8 – 27.2)	23.9 (18.2 – 30.3)
NPV (95% CI)	90.8 (87.3 – 93.5)	86.9 (83.4 – 89.9)
p-value	0.34	

Table1 – Baseline Characteristics

	All(625)	**NLR< 9.41(469)**	**NLR≥ 9.41(156)**	**p-value**	**MPV<11.3(453)**	**MPV≥11.3(172)**	**p-value**
Age, *years*	**60.72 (±12.14)**	60.08 (±12.00)	62.62 (±12.40)	0.02	60.25 (±12.34)	61.95 (±11.54)	0.11
BMI, *kg/m²*	**27.32 (±8.68)**	27.05 (±4.71)	26.63 (±5.12)	0.40	26.54 (±4.68)	27.93 (±5.00)	>0.01
Male	**422 (67.5)**	312 (66.5)	110 (70.5)	0.35	306 (67.5)	116 (67.4)	0.97
Hypertension	**369 (59.0)**	276 (58.8)	93 (59.6)	0.86	264 (58.3)	105 (61.0)	0.53
Diabetes	**148 (23.7)**	113 (24.1)	35 (22.4)	0.67	107 (23.6)	41 (23.8)	0.95
Smoking	**320 (63.1)**	251 (65.7)	69 (55.2)	0.03	237 (64.2)	83 (60.1)	0.39
Previous AMI	**56 (9.0)**	44 (9.4)	12 (7.7)	0.53	40 (8.8)	16 (9.4)	0.83
Previous PCI	**68 (10.9)**	55 (11.8)	13 (8.4)	0.24	51 (11.3)	17 (9.9)	0.63
Previous Stroke	**41 (6.6)**	33 (7.0)	8 (5.2)	0.41	28 (6.2)	13 (7.6)	0.53
Previous CKD	**23 (3.7)**	11 (2.3)	12 (7.7)	>0.01	16 (3.5)	7 (4.1)	0.75
Anterior AMI	**280 (44.8)**	207(44.2)	73 (46.8)	0.57	194 (42.8)	86 (50.3)	0.09
Hypotension	**60 (9.6)**	28 (6.0)	32 (20.5)	<0.001	38 (8.4)	22 (12.9)	0.09
Cardiac Arrest	**65 (10.4)**	34 (7.3)	31 (19.9)	<0.001	39 (8.6)	26 (15.2)	0.01
COPD	**24 (3.8)**	13 (2.8)	11 (7.1)	0.01	21 (4.6)	2 (1.7)	0.09
Killip III/IV	**74 (11.8)**	39 (8.3)	35 (22.4)	<0.001	46 (10.2)	28 (16.3)	0.03

LVFE≤35%	**58 (10.7)**	34 (8.5)	24 (14.4)	>0.01	34 (8.7)	24(16.1)	0.01
TIMI SCORE	**4 (2-6)**	3 (2-5)	5 (2.25-7)	>0.001	3 (2-5)	4 (2-7)	>0.01
ΔT, *hours*	**4.0 (2.5 – 6.4)**	4 (3-6.5)	4 (2.5-6)	0.49	4 (3-6)	4 (2.02-8.5)	0.35
NLR	**6.1 (3.84-9.41)**						
MPV	**10.7 (10 – 11.3)**						
Clinical and Procedural Characteristics							
Femoral Access	**196 (31.4)**	136 (29.1)	60 (38.5)	**0.02**	139 (30.8)	57 (33.1)	0.56
DES	**121 (19.4)**	86 (20.5)	25 (16)	0.22	86 (19.0)	35 (20.3)	0.70
Left main disease	**17 (2.6)**	10 (2.1)	7 (4.5)	0.11	12 (2.4)	5 (2.9)	0.85
Fluoroscopy Time, *min*	**14.3 (10.0-21.1)**	15.8 (9.7-21.1)	15 (10.5-21.8)	0.44	14 (10.0-20.2)	15 (10.2-23.0)	0.20
Contrast volume, *ml*	**170 (140-220)**	170 (140-230)	175 (145-200)	0.79	160 (140-210)	180 (150-250)	0.11

Values are expressed as mean (**SD** standard deviation), median (interquartile range) or number (%); **BMI** body mass index, **AMI** acute myocardial infarction, **PCI** percutaneous coronary intervention, **CKD** chronic kidney disease, **LVEF** left ventricle ejection fraction, **COPD** Chronic Obstructive Pulmonary Disease, **NLR** neutrophil-to lymphocyte ratio, **MPV** mean platelet volume, **DES** drug-eluting stents.

Table 2 – Relationship between high NLR and MPV and adverse events in univariate and multivariate analysis

Univariate Analysis					
ADVERSE EVENT		**NLR**		**MPV**	
	n(%)	***RR (95%CI)***	***p-value***	***RR (95%CI)***	***p-value***
During Procedure					
CIN	42(6.4)	2.27 (1.17 - 4.33)	0.01	1.20 (0.59 – 2.32)	0.59
Distal Embolization	35(4.9)	3.00 (1.43 - 6.24)	0.003	1.35 (0.64 – 2.74)	0.40
No-Reflow	46(6.5)	2.35 (1.25 - 4.35)	0.007	2.62 (1.40 - 4.92)	0.002
Complication in Procedure	117(16.5)	2.11 (1.35 - 3.27)	0.001	2.09 (1.36 - 3.21)	0.001
In-hospital					
Death	76 (10.6)	1.94 (1.13 – 3.26)	0.01	1.26 (0.71 – 2.17)	0.39
MACE	101(14.1)	1.96 (1.22 – 3.11)	0.004	1.73 (1.08 – 2.76)	0.02
Short and Long-term					
Mortality at 30 days	14(2.3)	0.26 (0.01 – 1.34)	0.20	0.87 (0.19 – 2.97)	0.84
MACE at 30 days	127(18.5)	0.56 (1.00 – 2.40)	0.04	1.25 (0.80 – 1.93)	0.31
Mortality at 1 year	65(12.7)	1.54 (0.89 - 2.61)	0.11	1.14 (0.64 - 1.95)	0.63
Multivariable Poisson Robust Regression Analysis					
No-Reflow		1.02 (1.00-1.04)	0.04[a]	1.34 (1.04 – 1.73)	0.02[a]
Complication in Procedure		1.01 (0.99-1.03)	0.08[b]	0.98(0.95 - 1.02)	0.53[b]
In-hospital MACE		1.01 (1.00-1.06)	0.02[c]	0.99 (0.95– 1.03)	0.76[c]

RR Relative Risk**, CI** Confidence Interval**, CIN** Contrast-induced nephropaty, **MACE** major cardiovascular outcomes,

Adjusted by:

[a] Drug Eluting Stent (DES), TIMI flow 2 or 3 after procedure, abciximab use, age, total length of stents;

[b] DES, TIMI flow 2 or 3 after procedure, abciximab use TIMI score, total length of stents, radiation;

[c] Age, Pain-to-door time, Creatinine pre-procedure, TIMI score, left ventricle ejection fraction < 35 before discharge, number of vessels

6. SEGUNDO ARTIGO ORIGINAL

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Temporal pattern of neutrophil-to-lymphocyte ratio in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention

Short title: Temporal pattern of NLR in patients in STEMI

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To the Editors,

In ST- elevation myocardial infarction (STEMI), neutrophil-to-lymphocyte ratio (NLR) has proven to be an independent predictor for procedural complications and worse clinical outcomes for short and long-term[1–3]. To date, no study has assessed the temporal patterns of NLR in patients with STEMI who underwent primary PCI. Therefore, the aim of this brief analysis was to evaluate the temporal trends of NLR in patients with STEMI who underwent primary percutaneous coronary (PCI).

Methods

This was a prospective single-center cohort study, which included consecutive patients with STEMI who underwent primary PCI in a tertiary university hospital (with 24-hour primary PCI service) in southern Brazil, between April 2011 and February 2018. STEMI was defined as typical chest pain at rest associated with ST-segment elevation of at least 1 mm in two contiguous leads in the frontal plane or 2 mm in the horizontal plane, or typical pain at rest in patients with a new, or presumably new, left bundle-branch block.

Blood samples were collected by venipuncture before the procedure as part of routine patient care and outpatient follow-up Neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing neutrophil count from lymphocyte count, both obtained from the same blood sample. Blood parameters were analyzed by the XE 5000 (Sysmex®, Norderstedt, Germany). More details about study subjects, procedural information, data collection, and clinical definitions, exclusion criteria and ethical guidelines are described elsewhere. [2]

Statistical Analysis

Continuous variables were expressed as mean (± standard deviation) or median (interquartile range [IQR]). Categorical variables were represented by their relative and absolute frequencies. The hypothesis that patients who died or had an adverse event

would have a greater NLR than those who remained alive and did not have any adverse event. Temporal trends were tested using the Kruskal-Wallis one-way analysis of variance by rank for non-normally distributed values. All statistical analyses were conducted using SPSS Statistics for Windows, Version 21.0., IBM Corp., Armonk, NewYork, USA.

Results

Between April 2011 and February 2018, 550 consecutive patients presenting with STEMI were enrolled in our registry. Fifteen subjects were excluded. Therefore, 535 patients were included in the final analysis. **Table 1** shows baseline and procedural characteristics of patients. In-hospital death and MACCE occurred in 11% and 13.8% of patients, respectively and 30-day death and MACCE occurred in 13.1% and 17.4% of the cases, respectively.

NLR was assessed over 72h after procedure during the in-hospital stay. There was significant variation over the period $p<0.0001$. Patients who died or had MACCE had an acute increase of NLR levels with a peak in at 48h after primary PCI reaching normal values at 6 months. Otherwise, patients with no adverse event have a consistent decrease of NLR levels reaching a plateau at 30 days (**Figure 1).**

Discussion

To our knowledge, this was the first time that long-term temporal trends of NLR are consistently evaluated. As previously described in the literature, patients with higher values of NLR have an increased risk of developing procedure complications, in-hospital, short and long-term MACCE[1,3,4].

There are limited data regarding NLR values in healthy population. Forget et al[5] has studied 413 healthy individuals to determine a normal cut-off value, with values ranging from 0.78 to 3.53. They reassessed values after 48h and found that values

remained stables. Recently, another cohort study by Kim and colleagues[6] suggested that NLR increases over time in individuals with cardiovascular disease and reaches a maximum value around the time of an adverse event. In our studied population, after the main event there was a consistent decrease in NLR levels in patients who didn't have any complication, corroborating these findings by Kim[6] et al. that the higher levels occur in the adverse event. Likewise, patients who had a worse clinical response had an acute increase in the first 48h after procedure.

In the long term, the patients who had a good clinical response had a consistent decrease in NLR reaching values near the range suggested by Forget [5] as a normal range within 30-days. Patients with and adverse but survived, also had a decreased after the in-hospital phase, reaching the values near normal range at 6 months. These findings of higher NLR levels might reflect a sustained pro-inflammatory status favoring the pathogenesis of atherothrombotic coronary events.

In conclusion, this study describes important trends and patterns of NLR in patients with STEMI who underwent primary PCI. NLR was higher in patients who developed worse clinical outcomes with an acute peak 48h after primary PCI, and slowly decreasing until 6 months after the procedure, while patients with a good clinical response had a consistent decrease of NLR starting 24h after procedure to reach stable levels at 30 days. These results provide an important foundation for further research and may assist to evaluate clinical response in STEMI treatment strategies.

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Figure 1 - Temporal patterns of NLR levels according the occurrence of adverse events. A - In-hospital mortality; B – In-hospital death; C- 30-day mortality; D – 30-day MACCE.

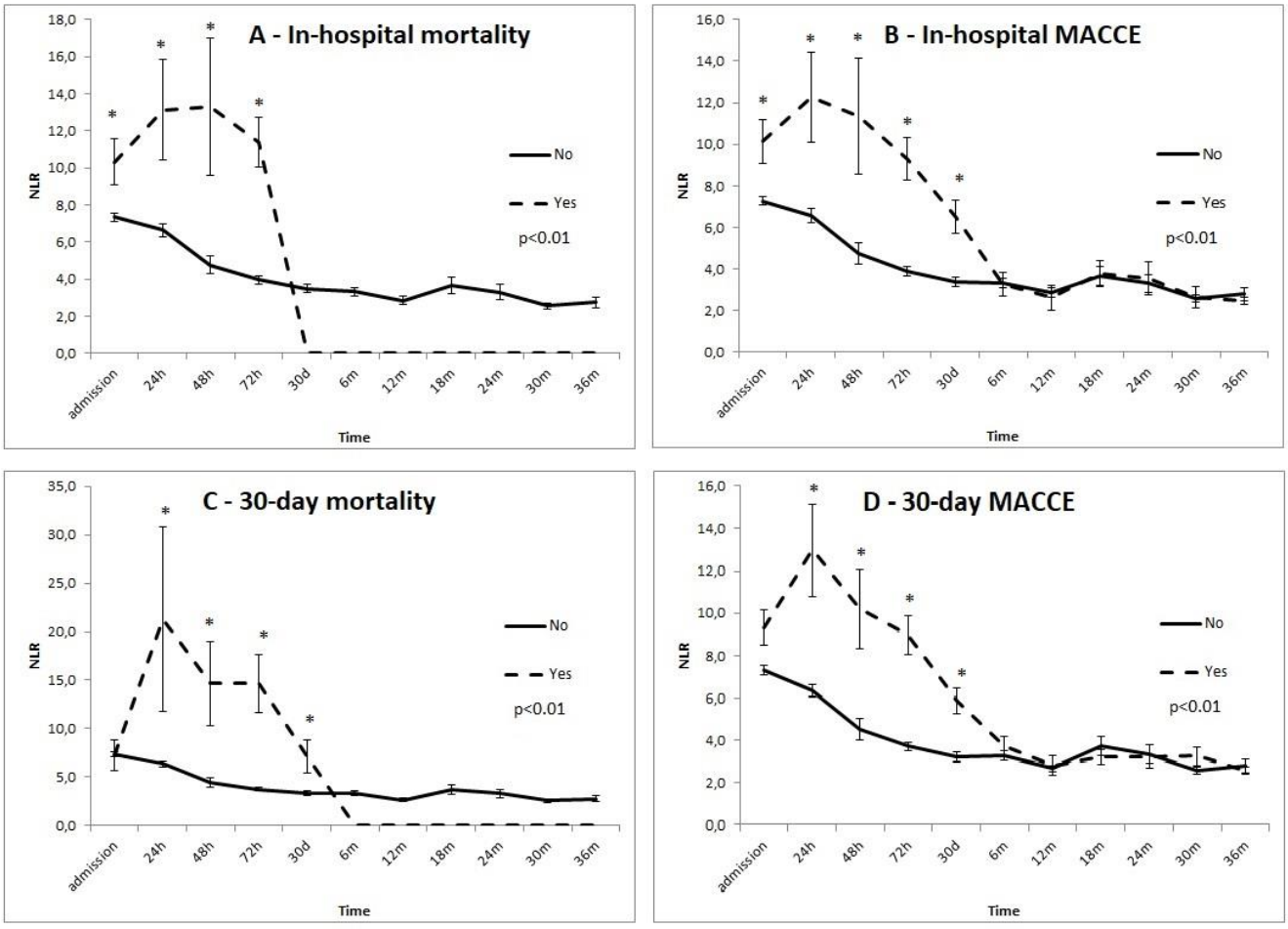

Table1 – Overall baseline characteristics and procedural characteristics according to in-hospital mortality

Clinical Characteristics	**All (535)**	**Alive (487)**	**Dead (48)**	***p*-value**
Age, *years*	60.34 (± 12.21)	59.73 (± 11.83)	66.56 (± 14.33)	<0.01
BMI, *kg/m²*	27.18 (± 5.75)	27.21 (± 5.0)	26.66 (± 13.0)	0.83
Male	339 (66.4)	313 (64.3)	26 (54.2)	0.16
Hypertension	335 (62.6)	305 (62.6)	30 (62.5)	0.98
Diabetes	133 (24.9)	119 (24.4)	14 (29.2)	0.46
Smoking	345 (64.5)	315 (64.7)	30 (62.5)	0.76
Previous AMI	49 (9.2)	45 (9.3)	4 (8.3)	0.83
Previous PCI	59 (11.1)	54 (11.1)	5 (10.4)	0.88
Previous Stroke	32 (6.0)	28 (5.8)	4 (8.3)	0.47
Previous CKD	19 (3.6)	10 (2.1)	9 (18.8)	<0.001
Anterior AMI	235 (43.9)	209 (42.9)	26 (54.2)	0.13
Hypotension	62 (11.7)	39 (8.1)	23 (47.9)	<0.001
Cardiac arrest	56 (10.5)	37 (7.6)	19 (39.6)	<0.001
COPD	21 (3.9)	18 (3.7)	3 (6.3)	0.38
Killip III/IV	58 (10.8)	33 (6.8)	25 (52.1)	<0.001
LVFE<40%	100 (21.8)	87 (20.1)	13 (50.0)	0.001
TIMI SCORE	4 (2 - 6)	3 (2 - 5)	7 (5 - 9)	<0.001
ΔT, *hours*	4.0 (2.5 – 6.0)	4 (2.5 – 6.0)	5 (2.7 – 8.0)	0.09
Leukocyte, *x10³µL*	11.9 (9.6 - 15.2)			
Neutrophils, *x10³µL*	9.4 (7.2 - 12.3)			
Lymphocyte, *x10³µL*	1.6 (1.1 - 2.1)			
NLR	6.0 (3.7 - 9.4)			
Procedural Characteristics				

Femoral access	198 (37.1)	163 (33.5)	35 (72.9)	<0.001
DES	55 (10.4)	52 (10.7)	3 (6.7)	0.39
Left main disease	13 (2.4)	11 (2.3)	2 (4.2)	0.41
Fluoroscopy time, *min*	14.4 (10.0 - 21.2)	14.1 (9.6 - 21.0)	18.2 (11.8 - 31.6)	0.04
Contrast volume, *ml*	180 (140 - 230)	170 (140 - 220)	210 (180 - 300)	<0.001

Values are expressed as mean (± standard deviation), median (interquartile range) or number (%); **BMI** body mass index, **AMI** acute myocardial infarction, **PCI** percutaneous coronary intervention, **LVEF** left ventricle ejection fraction, **CKD** chronic kidney disease, **COPD** Chronic obstructive pulmonary disease, **DES** drug-eluting stents.

7. TERCEIRO ARTIGO ORIGINAL

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Long-term pattern of red cell distribution width in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention

Short Title: Trends of red cell distribution width after STEMI

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Abstract

Red cell distribution width (RDW) is an indirect marker of inflammation and an independent predictor of long-term mortality. The aim of this study was to determine RDW values in patients with ST-elevation acute myocardial infarction (STEMI) submitted to primary percutaneous coronary intervention (PCI) and evaluate its association with adverse outcomes. We measured RDW in STEMI patients before undergoing primary PCI and divided into low and high RDW. Patients were followed-up to 3 years after their discharge for the occurrence of in-hospital, 30-days and long-term major adverse cardiovascular events (MACE) and mortality. We included 485 patients with a mean age of 61.1(±12.5) years, 62.9% were male. In multivariate analysis, RDW remained independent predictor of long-term mortality and MACE (relative risk [RR] 1.51; 95% confidence interval [95%CI] = 1.11-2.05; p=0.007 and RR = 1.42; 95%CI = 1.30 – 1.82; p=0.004. Area under the curve for long-term mortality was 0.65(95%CI=0.61-0.69;p<0.0001). RDW<13.4 had a negative predictive value of 87.4% for all-cause mortality. Patients who had worse outcomes remained with higher values of RDW during the follow-up. In conclusion, high RDW is an independent predictor of long-term mortality and MACE in patients with STEMI undergoing primary PCI. A low RDW has an excellent negative predictive value for long-term mortality. Patients with sustained elevated levels of RDW have worse outcomes at long-term follow-up.

KEYWORDS: Myocardial infarction; percutaneous coronary intervention; biomarkers; red cell distribution width

1. Introduction

Since inflammation plays a central role in atherosclerosis and acute coronary syndromes, several inflammatory markers have been proposed to assess cardiovascular risk in patients with MI. Recently we demonstrated that neutrophil-to-lymphocyte ratio (NLR), another blood count derivative surrogated inflammatory marker, is an independent predictor of in-hospital major cardiovascular adverse events (MACE) and procedural complications in patients with ST-elevation acute myocardial infarction (STEMI) submitted to primary percutaneous coronary intervention (PCI)[1].

Red blood cell distribution width (RDW) is a numerical measure of the variability in size of circulating erythrocytes. Elevated RDW values are associated with increased risk of coronary artery disease possibly because it reflects the bone marrow's response to systemic ongoing inflammation [2]. Because RDW is promptly available in routine blood count analysis, it may be used as a cost-effective predictor of inflammation and cardiovascular complications.

To date, few studies have assessed the association between RDW and the occurrence of long-term outcomes after primary percutaneous coronary intervention (PCI)[3–7]. However, studies with larger samples showing RDW discriminative ability and diagnostic accuracy are lacking and, to date, no study assessed the long-term pattern of this hematologic parameter of inflammation. The objective of the present study was to investigate the temporal pattern and prognostic value of RDW for long-term adverse events in patients presenting with STEMI submitted to primary PCI.

2. Methods

2.1 Research subjects

This was a prospective single-center cohort study, in which we included consecutive patients with STEMI submitted to primary PCI in a tertiary university hospital with a 24-hour primary PCI service in southern Brazil, between April 2011 and March 2018. STEMI was defined as typical chest pain at rest associated with ST-segment elevation of at least 1 mm in two contiguous leads in the frontal plane or 2 mm in the horizontal plane, or typical pain at rest in patients with a new, or presumably new, left bundle-branch block. Exclusion criteria were the lack of laboratory tests at admission, follow-up or not have been submitted to primary PCI. This study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Institutional Research and Ethics Committee and written informed consent was obtained from all individual participants included in the study.

2.2 Study protocol

Blood samples were collected by venipuncture and blood count was assessed as other blood tests routinely performed in patients admitted with STEMI. RDW is a numerical measure of the variability in size of circulating erythrocytes and its value is automatically available in blood count analysis. Medical and interventional management of STEMI patients throughout hospitalization and after discharge were based on guideline recommendations and are described elsewhere[8]. Posterior blood samples were made at 30 days, 6, 12, 18, 24, 30 and 36 months during clinical visit. Blood parameters were analyzed by the XE 5000 (Sysmex®, Norderstedt, Germany).

Data from medical records were transferred to standardized case report forms (CRFs). Data collected included: baseline clinical characteristics, medical history, procedure characteristics, reperfusion strategy, initial and final thrombolysis in myocardial infarction (TIMI) flow grade, and discharge therapies. In-hospital and thirty-

day mortalities rates were also recorded in the CRF. Thirty-day and 3-year follow-up were ascertained by clinical visit or telephone contact with patients or their families.

2.3 Outcome definitions

Major cardiovascular events (MACE) were defined as death from any cause, new MI, stent thrombosis and Stroke 30 days after primary PCI. New MI was defined as recurrent chest pain with ST-segment elevation or new Q waves or a raise of serum biomarkers after their initial decrease. Stroke was defined as a new, sudden-onset focal neurological deficit, of a presumably cerebrovascular cause, irreversible (or resulting in death) and not caused by other readily identifiable causes. Contrast-induced nephropathy was a raise of 0.3 mg/dL or 50% in post-procedure (24–72 h) creatinine compared to baseline, proposed by the Acute Kidney Injury Network (AKIN) as a standardized definition of acute kidney injury.

2.4 Statistical Analysis

Continuous variables were expressed as mean (±standard deviation) or median (interquartile range [IQR]) based on–their symmetrical or asymmetrical distribution, respectively. The normality of the distribution of each variable was assessed by using Shapiro-Wilk test. Categorical variables were represented by their relative and absolute frequencies. Patients were separated into tertiles on the basis of their serum RDW on admission. The hypothesis that patients in the highest RDW tertile would have a greater event rate than those in the other tertiles was tested using a chi-square test and adjusted relative risk (RR). Receiver-operating characteristic (ROC) curves were used to evaluate the discriminatory power of the different scores. Youden index analysis was performed

to determine the best cutoff value of RDW for predicting clinical endpoints. Multivariate analysis was performed by Poisson robust regression in order to evaluate the independent predictive value of RDW. P-value was considered significant at <0.05. Temporal Trends was tested by generalized estimating equation with a Bonferroni post hoc analysis. C-statistic analysis and Kaplan–Meier methods with a comparison with the use of the log-rank test were made using MedCalc Statistical Software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium). All remaining statistical analyses were conducted SPSS Statistics for Windows, Version 21.0. (IBM Corp., Armonk, NewYork, USA).

3. Results

Between April 2011 and March 2017, 551 consecutive patients presenting with STEMI were enrolled in our registry. Sixty-six subjects were excluded due to loss of follow-up, lack of laboratory tests or failure to perform primary PCI, therefore 485 patients were included in the final analysis, with a mean follow-up of 29 months. Patients were divided into two groups: high RDW and low RDW, where high was defined as above 75th percentile or ≥14. Overall mean age was 61.1(±12.5), 62.9% were male, 62.3% had hypertension 26% had diabetes and RDW median value was 13.4 (IQR 12.9-14). **Table 1** shows baseline clinical and procedural characteristics of patients. Death occurred in 11.5% of patients before hospital discharge, 13.6% after thirty days and in 21.4% at the end of 3 years.

In univariate analysis patients with higher values of RDW had a significantly greater risk of in-hospital death, in-hospital MACE, 30-day MACE and long-term all-cause mortality **(Table 2).** In multivariate analysis (adjusted by age, anterior wall MI, Killip 3/4, left ventricle ejection fraction (LVEF) ≤ 35% after discharge, hypotension at admission, previous MI, hypertension, chronic kidney disease, pain-to-door time, baseline creatinine, hemoglobin, number of vessels, contrast volume, TIMI score) RDW

remained independent predictor of long-term all-cause mortality and MACE (relative risk [RR] 1.51; 95% confidence interval [95%CI] = 1.11-2.05; *p*=0.007 and RR = 1.42; 95%CI = 1.30 – 1.82; *p*=0.004) **(Table 3).**

Figure 1 shows the incidence of long-term all-cause mortality and MACE according to quartiles of RDW. At the end of 3-year follow-up, the rate of death from any cause and MACE was 34.8% and 43.7% in high RDW group, as compared with 16.3% and 23.7% in low RDW group, respectively (hazard ratio [HR] = 2.3; 95%CI = 1.48 - 3.59; *p*<0.0001 and HR = 2.08; 95%CI = 1.39 – 3.11; *p*<0.0001)(**Figure 2 & 3).**

Figure 4 presents the ROC curves and diagnostic test evaluation of long-term all-cause mortality and MACE with an AUC of 0.65 (95%CI = 0.61-0.69; *p*<0.0001) and 0.62 (95%CI = 0.58 – 0.67; *p*<0.0001), respectively. An RDW value higher than 13.4, obtained through Youden's index, yielded a sensitivity of 70.1%, a specificity of 56.4%, diagnostic accuracy of 70%, with a positive predictive value of 30.5% for long-term mortality. A lower than 13.4 RDW value had a negative predictive value of 87.4%. Data regarding the medians of RDW during follow up is presented in **Figure 5**.

4. Discussion

In the present study of STEMI patients undergoing primary PCI, we have found that red blood cell distribution width (RDW) measurement is excellent to identify patients at high risk of long-term mortality. To the best of our knowledge, this was the first time that the prognostic value of RDW was consistently discriminated in longer follow-up periods.

Evidence of the prognostic value of RDW in patients with STEMI is scarce. High admission RDW values have been previously found to be an independent predictor of adverse cardiovascular outcomes after MI treated with primary PCI [3,5–7,9]. Isik et al [6] have

found an area under the curve (AUC) for mortality of 0.83 with an RDW threshold of 13.8 (sensitivity: 80%, specificity: 64%) in patients with STEMI submitted to primary PCI. Our results showed an AUC with moderate discriminatory power of 0.65 in RDW values above 13.4%. Despite a moderate sensitivity of 70.1% and specificity of 56.4%, a low RDW had an excellent negative predictive value of 87.4% for all-cause mortality at 3 years. However, we have found no significant association between RDW levels and in-hospital mortality or other short-term outcomes. Beyond a well-known relationship between increased RDW and other conditions with prognostic importance such as low ejection fraction and impaired renal function[10,11], our findings support that RDW remains an independent predictor of long-term mortality even after multivariate adjustment.

The mechanism underlying the pathophysiology by which RDW is associated with poor prognosis is not clear. The main hypothesis relies on a consequence of inflammatory stress leading to impaired bone marrow production of blood cells and platelet activation[12]. These findings are supported by Lippi and colleagues[13] which have observed a relationship between high RDW values and increased levels of C-reactive protein and erythrocyte sedimentation rate. In addition, inflammatory cytokines such as TNF-α, IL-1, and IL-6 appear to suppress the maturation of erythrocytes in the bone marrow causing them to enter immature into the bloodstream. Ferrario *et al.*[14] observed that plasma erythropoietin levels increase in patients with STEMI and last up to 7 days after the event compared to controls. The fact that erythropoietin and thrombopoietin have a considerably similar structure and high levels of erythropoietin may lead to an increase in platelet reactivity[15] is another evidence supporting this association between RDW and inflammation.

Altered measures of RDW may be related to iron-deficiency anemia, which is associated with poor prognosis in patients with both stable and unstable coronary artery

disease (CAD)[16,17]. Patients with anemia have myocardial ischemic damage due to decreased content of oxygen supplying the myocardium[18], a higher cardiac output to maintain appropriate systemic oxygen delivery[19] and an impaired coronary microcirculation[20]. Also, anemia is associated with chronic kidney disease and other chronic/inflammatory disorders that may contribute to impaired survival. Nevertheless, our findings remained significant even after adjustment of admission hemoglobin levels.

Data regarding RDW normal values in STEMI patients vary in the literature, but RDW of at least 13.6% is considered elevated[4]. Besides, there was no information about RDW behavior and fluctuations in long-term follow-up. Our patients with high admission RDW were older and had multiple comorbidities such as hypertension, chronic kidney disease, and ventricular dysfunction more often. The incidence of mortality across the quartiles increased significantly from 14.0 to 34.8% and the patients who died during follow-up had a higher sustained or even an increase of RDW values. These findings reflect the pro-inflammatory status of higher-risk patients in the pathogenesis of atherothrombotic coronary events.

In our analysis, some strengths and limitations deserve to be highlighted. This study has limitations that are inherent to the nature of observational studies. Some data were obtained retrospectively, which can determine less reliable information. In addition, we do not have the results of tests that can affect RDW levels such as folic acid, vitamin B12, iron, eritropoeitin levels and liver function. However, this study consisted of consecutive and unselected patients from a tertiary referral hospital, therefore highly applicable in daily clinical practice.

5. Conclusions

In conclusion, elevated baseline RDW levels independently predicted long-term MACE and all-cause mortality in a cohort of patients with STEMI submitted to primary

PCI. Also, sustained higher RDW levels were also related to worse outcomes, reflecting a pro-inflammatory state. A low RDW has an excellent negative predictive value and may be an useful and inexpensive tool to be used at bedside. Association between RDW, inflammation and cardiovascular outcomes is undeniable, and targeting RDW in therapeutic management of CAD may be subject of future research.

Conflict of interest: The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Funding: The work was supported by the authors.

Informed consent: Informed consent was obtained from all individual participants included in the study.

List of abbreviations: RDW: Red cell distribution width; STEMI: ST-elevation acute myocardial infarction; PCI: percutaneous coronary intervention; MACE: major adverse cardiovascular events; RR: relative risk; CI: confidence interval; NLR: neutrophil-to-lymphocyte ratio; CRF case report forms; TIMI: thrombolysis in myocardial infarction; AKIN: acute kidney injury network; IQR: interquartile range; ROC: receiver-operating characteristic; AUC: area under the curve; HZ: hazard ratio; CAD: coronary artery disease

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Microcirculation and Clinical Outcomes in Patients With ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention. *Int Heart J*. 2015;56(4):381-388. doi:10.1536/ihj.15-006

Figure 1 – Incidence of long-term MACE and all-cause mortality according to quartile of RDW**.**

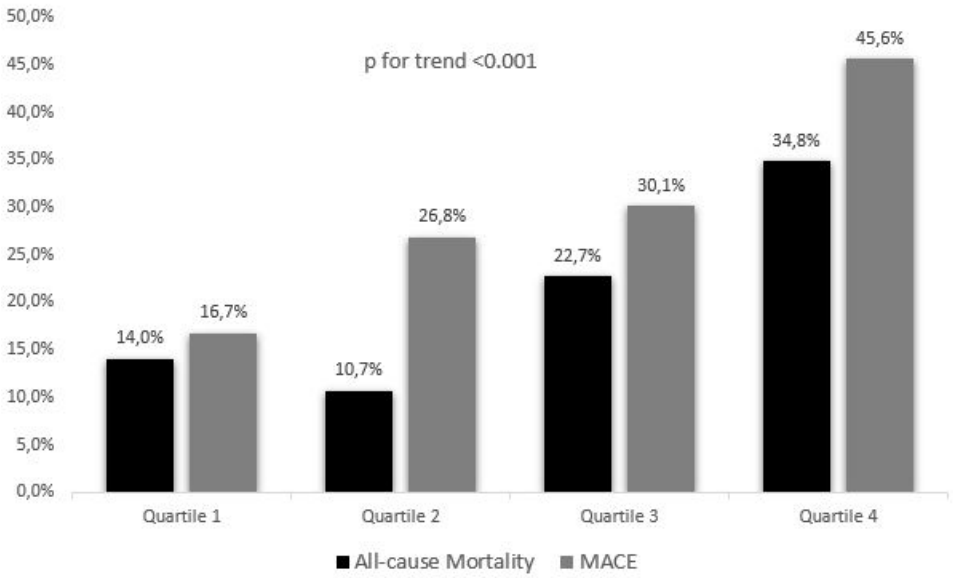

Figure 2 – Time-to-Event Curves for long-term all-cause mortality. Event rates were calculated with the use of Kaplan–Meier methods and compared with the use of the log-rank test.

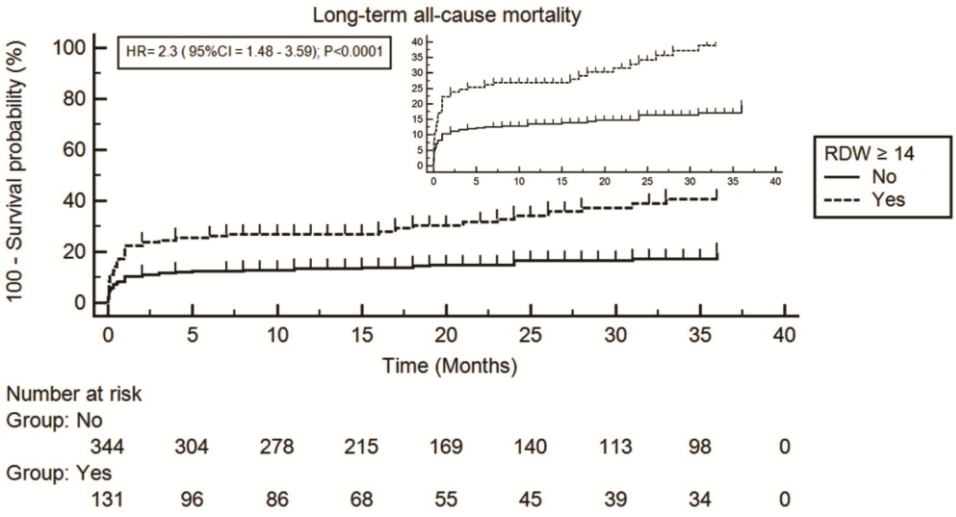

Figure 3 – Time-to-Event Curves for long-term MACE. Event rates were calculated with the use of Kaplan–Meier methods and compared with the use of the log-rank test.

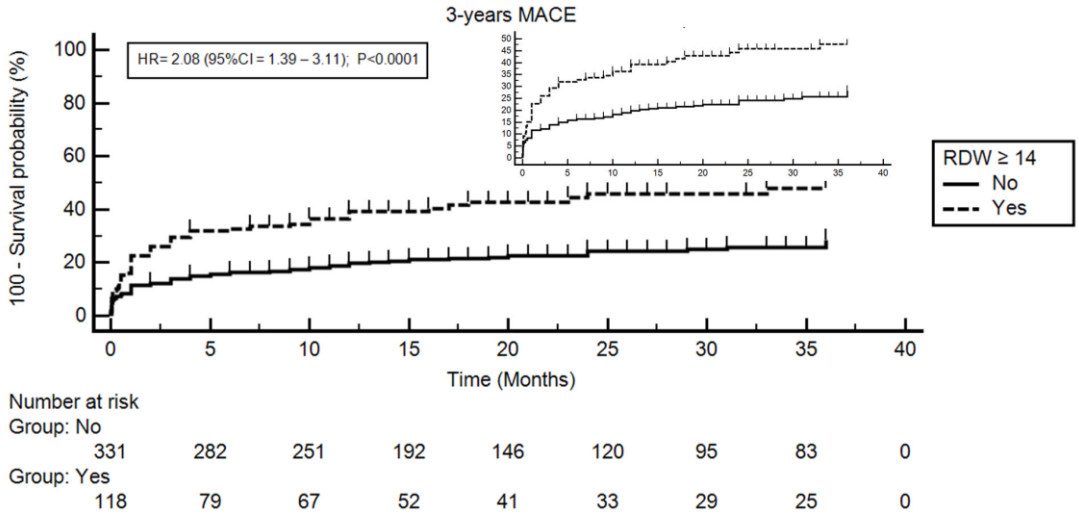

Figure 4 – Receiver operator characteristic (ROC) graphic showing areas under the curve (AUC) of red cell distribution width (RDW) for long-term MACE and all-cause mortality.

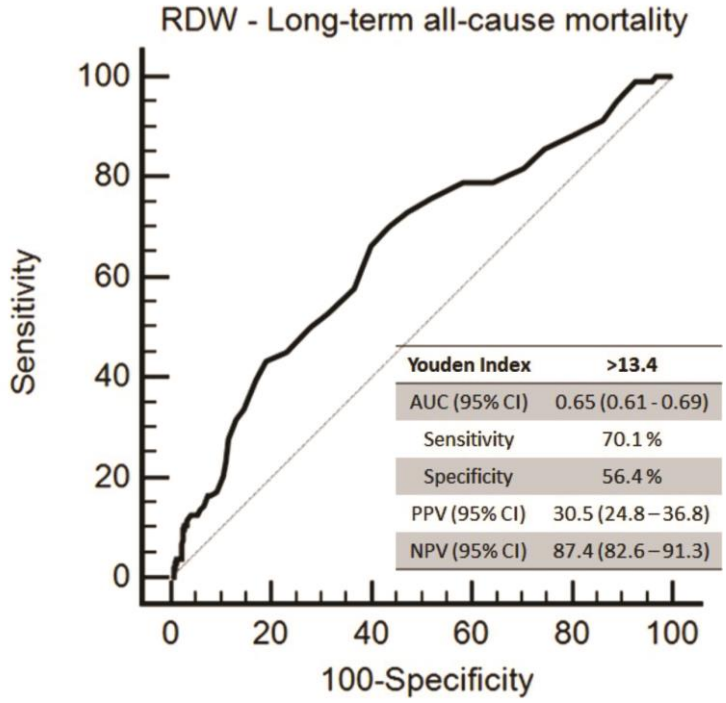

Figure 5 – Long-term trends of RDW value.

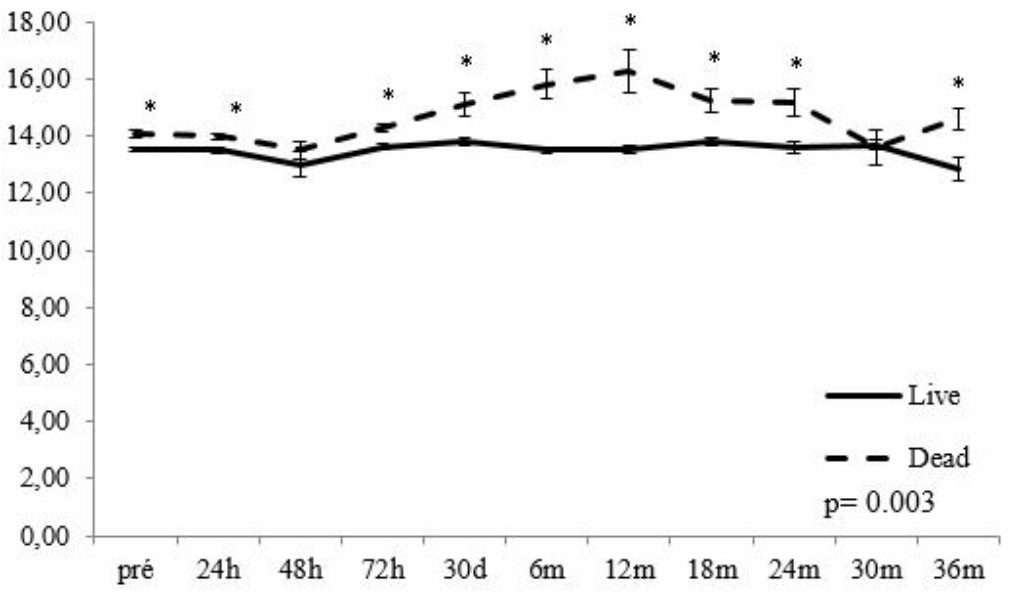

Table1 – Overall baseline characteristics and according to red cell distribution width (RDW)

	All(485)	**<14 (350)**	**≥14(135)**	***p*-value**
Demographic				
Age	61.11 (± 12.5)	60.1 (± 12.5)	63.5 (± 12.4)	<0.01
BMI, *kg/m²*	27.18 (± 5.7)	27.36 (± 5.9)	26.68 (± 5.1)	0.30
Male	305 (62.9)	227 (64.9)	78 (57.8)	0.14
Hypertension	302 (62.3)	208 (59.4)	94 (69.6)	0.03
Diabetes	126 (26.0)	92 (26.3)	34 (25.2)	0.80
Smoking	302 (62.3)	215 (61.4)	87 (64.4)	0.53
Previous AMI	47 (9.7)	29 (8.3)	18 (13.3)	0.08
Previous PCI	54 (11.1)	37 (10.6)	17 (12.6)	0.52
Previous Stroke	35(7.2)	24 (6.9)	11 (8.1)	0.60
Previous CKD	21 (4.3)	7 (2.0)	14 (10.4)	<0.0001
Anterior AMI	217 (44.7)	153 (43.7)	64 (47.4)	0.42
Hypotension	61 (12.6)	40 (11.4)	21 (15.6)	0.21
Cardiac arrest	59 (12.2)	41 (11.7)	18 (13.4)	0.61
COPD	22 (4.5)	13 (3.7)	9 (6.7)	0.16
Killip III/IV	65 (13.4)	38 (10.9)	27 (20.0)	<0.001
LVFE<35%	48 (11.5)	27 (8.8)	21 (19.1)	<0.01
TIMI SCORE	4.0 (2-6)	4 (2 - 6)	4 (3 - 8)	<0.01
ΔT	4 (2.5 – 6.4)	4.0 (2.5 – 6.0)	4.7(3.0 – 8.0)	0.01
Baseline Creatinine	0.89 (0.72-1.18)	0.87 (0.71 - 1.13)	0.98 (0.77 - 1.32)	0.01
Hemoglobin, *x10³µL*	13.2 (±2.2)	13.2 (±1.6)	13.1 (±3.1)	0.75
Hematocrit	39.8 (±14.5)	40.3 (±16.6)	38.6 (±6.34)	0.23
Platelet	232 (±73.1)	228 (±70.2)	243 (±79.3)	0.04
RDW	13.3 (12.8 - 14.0)			

Clinical and Procedural Characteristics				
Femoral access	189 (39.0)	123(35.1)	66(48.9)	<0.01
DES	59 (12.2)	43(12.3)	16(11.9)	0.89
Left main disease	11 (2.3)	7(2.0)	4(3.0)	0.52
Fluoroscopy time	14.4 (10.1 - 21.7)	14.3 (10.2 - 22)	15.0 (9.2 - 21.2)	0.62
Contrast volume	180 (140 - 240)	180 (140 - 250)	180 (180 - 250)	0.59

Values are expressed as mean (± standard deviation), median (interquartile range) or number (%); **BMI** body mass index, **AMI** acute myocardial infarction, **PCI** percutaneous coronary intervention, **LVEF** left ventricle ejection fraction, **CKD** chronic kidney disease, **COPD** Chronic Obstructive Pulmonary Disease, **DES** drug-eluting stents,

Table 2 - Relationship between high RDW and adverse events in univariate and multivariable Poisson robust regression analysis

		Univariate Analysis		Multivariable Analysis	
	n(%)	RR (95%CI)	p-value	Adjusted RR (95%CI)	Adjusted p-value[†]
In-hospital death	27(20.0)	2.76 (1.56 - 4.89)	<0.0001	1.03 (0.68 - 1.56)	0.86
In-hospital MACE	34(25.2)	2.60 (1.56 - 4.34)	<0.0001	1.09 (0.81 - 1.45)	0.55
30-day death	32(23.7)	3.27 (0.63 - 6.96)	<0.0001	1.21 (0.77 - 1.12)	0.56
30-day MACE	41(30.4)	2.50 (1.55 - 4.00)	<0.0001	1.27 (0.97 - 1.66)	0.07
Long-term all-cause mortality	47(34.8)	2.74 (1.74 - 4.32)	<0.0001	1.40 (1.05 - 1.87)	0.01

[†]Adjusted by age, anterior wall MI, Killip 3/4, LVEF ≤ 35% after discharge, baseline creatinine, hypotension at admission, pain-to-door time, hemoglobin, number of vessels, contrast volume, TIMI score.

RR Relative risk**, CI** Confidence Interval**, MACE** major cardiovascular outcomes.

8. QUARTO ARTIGO ORIGINAL

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Early vs. late neutrophil-to-lymphocyte ratio for the prediction of adverse outcomes in patients with STEMI undergoing primary PCI

Short Title: Late NLR predicts adverse outcomes in STEMI

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1. Introduction

Admission neutrophil-to-lymphocyte ratio(NLR) has been shown to predict adverse events in patients with ST-elevation Myocardial Infarction(STEMI)[1–3]. New evidence has shown that NLR keeps increasing within 48-72 hours in patients who develop worse outcomes[4]. Therefore, we aimed to compare the prognostic capacity of admission and late NLR for adverse events in patients with STEMI undergoing primary percutaneous coronary intervention(pPCI).

2. Methods

This was a prospective cohort study with consecutive patients admitted with STEMI, who underwent pPCI and were followed for 12 months. NLR was calculated by dividing neutrophil count from lymphocyte count obtained from the same blood sample. NLR was assessed at admission and 48-72 hours post-procedure(late NLR) as part of routine care. Other details about procedural information, data collection, clinical definitions, exclusion criteria, and ethical guidelines are described elsewhere[2]. High NLR was defined as above upper tertile. Receiver operating characteristic(ROC) curve analysis was performed to calculate the area under the curve(AUC) for the occurrence of short and long-term mortality and major adverse cardiovascular events (MACE). Multivariate analysis was performed by Poisson robust regression to evaluate the independent predictive value of late NLR. For the multivariate model, risk factors that were univariate predictors (at $p < 0.05$) were initially considered as factors or covariates. C-statistic analysis were compared with the De Long test and Kaplan–Meier methods with a comparison with the use of the log-rank test were made using MedCalc Statistical

Software version 14.8.1(MedCalc Software, Ostend, Belgium). All remaining statistical analyses were conducted using SPSS Statistics for Windows, v.21.0. (IBM Corp., Armonk, NewYork, USA).

3. Results

Between March 2011 and December 2018, 864 patients presented with STEMI in our institution, and 779 were included in the analysis. Mean age was 60.68 (±12), 66.4% were male, 62.1% had hypertension and 24% had diabetes.

In multivariate analysis, when adjusted by age, pain-to-door time, previous chronic kidney disease, previous MI, hypotension at admission, femoral access, fluoroscopy time, contrast volume TIMI score, left ventricle ejection fraction ≤40% before discharge, late NLR remained an independent predictor of in-hospital death, in-hospital MACE and 1-year mortality(relative risk[RR] = 14.9, 95% confidence interval[95% CI]= 3.4 - 80.35, *p*= 0.001; RR= 3.4, 95%IC= 1.2 – 9.1, *p* = 0.01; RR= 7.6, 95%IC= 2.9 – 26.1, *p*= 0.01, respectively). The use of late NLR increased significantly the AUC of in-hospital mortality from 0.55 to 0.84(Sensitivity 81.2%, Specificity 75.6%, Positive Predictive Value 24.5 and Negative Predictive Value 97.7). Discriminative data of other outcomes are described in **Figure 1**. At the end of 1-year follow-up, the rate of death from any cause was 28.6% in high late NLR group, hazard ratio [HR] = 3.07 (95%CI = 1.96 - 4.8); p < 0.0001; **Figure 2**).

4. Discussion

In this present cohort-based study of STEMI patients undergoing pPCI, late NLR was strongly associated with short and long-term mortality and MACE. Moreover, late NLR increase admission NLR prognostic capacity for adverse events in these

patients. To our knowledge, this was the first time late NLR was consistently evaluated in this setting.

Normal distribution of NLR is still a matter of debate. Forget et al.[5] have studied healthy individuals and values ranged between 0.78 and 3.5, remaining stable after 48 hours. Recently, Kim[6] and colleagues observed that NLR increases over time in individuals with cardiovascular disease, reaching peak values around the time of an adverse event. A recent study from showed that patients who experienced adverse outcomes during follow-up had an acute increase in NLR values 48h after procedure[4]. These results support the findings of Kim et al.[6] described above.

On the present study, when late NLR values were used to assess the ability to predict adverse events there was a significant increase in AUC compared to admission NLR. This might be explained because neutrophils are the first leukocytes to infiltrate the infarcted myocardium releasing a variety of proteolytic enzymes which cause plaque rupture, infarct expansion, coagulation pathway activation, and cardiac electrical instability[7–9]. In addition, there is evidence for prolongation of the lifespan of neutrophils in unstable plaques[10]. In contrast to increased neutrophils in damaged myocardial area, lymphocytes decrease due to increased levels of cortisol, catecholamines and proinflammatory cytokines in acute STEMI[11,12]. This suggests that the exacerbated inflammatory response after the event defines the worse outcome for these patients.

In the clinical practice of most centers worldwide white blood counts are routinely obtained during hospitalization for an acute coronary event. In the present study, a measurement of 48-72h NLR was a strong predictor of adverse outcomes, which highlights a potential application of this inexpensive and readily available inflammatory marker for risk stratification post-myocardial infarction.

4. References

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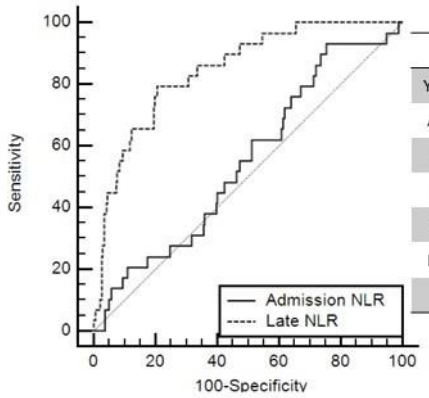
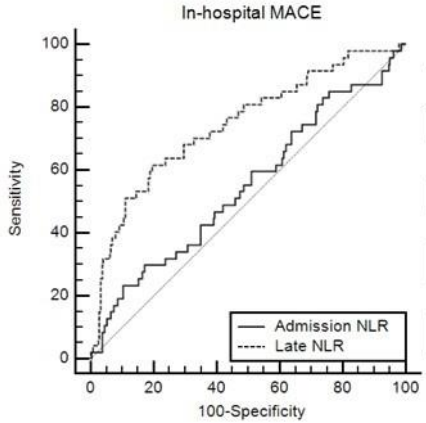
Figure 1 – Receiver operator characteristic (ROC) graphic showing areas under the curve (AUC) of admission neutrophil–to–lymphocyte ratio (NLR) and late NLR for (A) in-hospital death, (B) in-hospital major cardiovascular outcomes (MACE), (C) 1-year all-cause mortality and (D) 1-year MACE.

In-hospital death



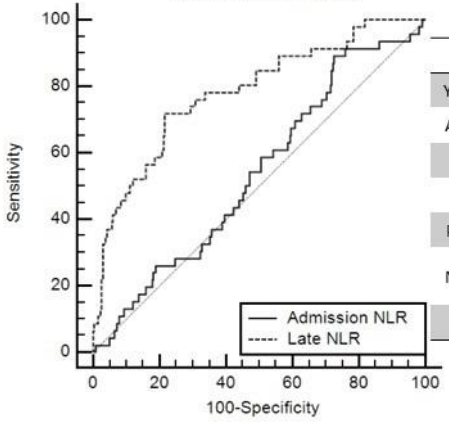
	Admission NLR	Late NLR
Youden Index	>9.35	>5.45
AUC (95% CI)	0.55 (0.49 - 0.60)	0.84 (0.80 – 0.88)
Sensitivity	38.8 %	81.2%
Specificity	76.7 %	75.6%
PPV (95% CI)	15.2 (10.2 – 21.5)	24.5 (16.7 – 33.8)
NPV (95% CI)	92.1 (89.5 – 94.3)	97.6 (94.9 – 99.1)
p-value	<0.0001	

In-hospital MACE



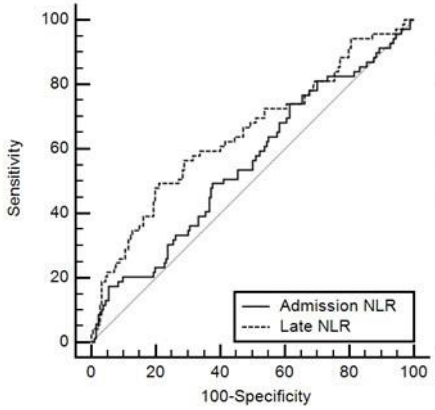
	Admission NLR	Late NLR
Youden Index	>9.35	>5.45
AUC (95% CI)	0.55 (0.49 - 0.60)	0.74 (0.69 – 0.79)
Sensitivity	38.7 %	62.3%
Specificity	77.4 %	77.3%
PPV (95% CI)	21.1 (15.2 – 27.9)	35.8 (26.8 – 45.7)
NPV (95% CI)	89. (86.0 – 91.6)	91.0 (86.8 – 94.2)
p-value	<0.0001	

1 year all-cause mortality



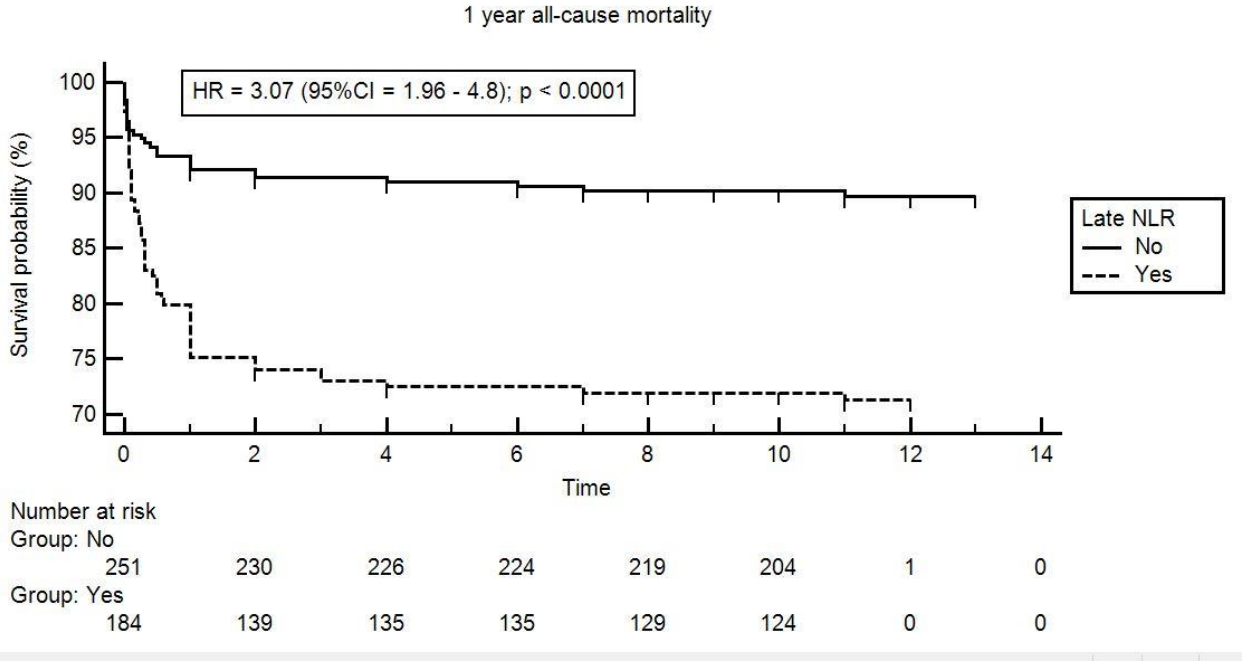
	Admission NLR	Late NLR
Youden Index	>5.8	>5.44
AUC (95% CI)	0.56 (0.53 - 0.59)	0.77 (0.72 – 0.82)
Sensitivity	64.1 %	70.8%
Specificity	48.9 %	77.2%
PPV (95% CI)	19.2(15.7 – 23.2)	35.4 (25.9 – 45.8)
NPV (95% CI)	87.8 (84.2 – 90.9)	93.7 (89.6 – 96.5)
p-value	<0.0001	

1 year MACE



	Admission NLR	Late NLR
Youden Index	>2.05	>5.44
AUC (95% CI)	0.55 (0.49 - 0.61)	0.64 (0.58 – 0.70)
Sensitivity	84.0 %	47.4 %
Specificity	7.52 %	76.8 %
PPV (95% CI)	24.5 (21.0 – 28.4)	41.1 (30.8 – 52.0)
NPV (95% CI)	56.9 (43.2 – 69.8)	81.1 (75.3 – 86.1)
p-value	0.16	

Figure 2 – Time-to-Event Curves for 1 year all-cause mortality for late NLR. Event rates were calculated with the use of Kaplan–Meier methods and compared with the use of the log-rank test



9. CONCLUSÕES E CONSIDERAÇÕES FINAIS

Os parâmetros hematológicos analisados - NLR, VPM e RDW - se mostraram eficazes para predizer o risco de eventos adversos cardiovasculares na síndrome coronariana aguda com supradesnivelamento do segmento ST.

O presente estudo identificou a NLR como preditora independente de ECAM intra-hospitalar em pacientes com IAMCSST submetidos à ICP primária. Além disso, o RDW se mostrou preditor independente de ECAM e mortalidade a longo prazo. O VPM não se mostrou preditor independente para ocorrência de ECAM ou de mortalidade, apenas preditor independente para ocorrência de *no-reflow*, juntamente com a NLR.

Foi observado que, em pacientes que sofriam eventos adversos, a NLR aumentava dentro de um período de 48 a 72 horas, enquanto nos demais ocorria um descenso constante até atingir um platô dentro de 30 dias. Esse valor, determinado de NLR tardia, se manteve preditor independente de ECAM e mortalidade intra-hospitalar, além de mortalidade a longo prazo. Além disso, quando utilizada a NLR tardia, houve um aumentou significativo da AUC para os desfechos analisados.

Dentre os parâmetros analisados, a NLR da admissão, a NLR tardia e o VPM mostraram-se marcadores para complicações agudas, enquanto a NLR tardia e o RDW estiveram correlacionados com complicações a longo prazo.

Na prática clínica, o hemograma completo, incluindo a contagem de plaquetas, é realizada rotineiramente durante a hospitalização, especialmente de pacientes com síndrome coronariana aguda. Por ser um exame altamente disponível na pratica clínica, com custo acessível e prático, sem necessidade de

especialistas para interpretação, esses parâmetros podem ser mais uma ferramenta a ser utilizada à beira do leito para ajudar a identificar pacientes com pior prognóstico.

10. ANEXO I

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Nº do projeto GPPG: 15-0557

Título do Projeto: Coorte de Pacientes com Infarto Agudo do Miocárdio Atendidos no Hospital de Clínicas de Porto Alegre

Você está sendo convidado(a) a participar de uma pesquisa cujo objetivo é obter maior conhecimento a respeito das características dos pacientes com diagnóstico de infarto agudo do miocárdio e submetidos à angioplastia coronariana e das características deste procedimento realizado no hospital. Esta pesquisa está sendo realizada pelo Serviço de Hemodinâmica do Hospital de Clínicas de Porto Alegre (HCPA). Dessa forma, estamos realizando este convite porque você realizou o procedimento de angioplastia coronariana no HCPA.

Se você aceitar participar da pesquisa, os procedimentos envolvidos em sua participação são os seguintes:

A equipe de pesquisa realizará o preenchimento de uma ficha de registro baseada nos dados de seu prontuário do hospital contendo informações sobre seu estado de saúde atual, resultados de exames e descrição de procedimentos. Por isso, solicitamos a sua autorização para este acesso.

Após 30 dias da alta hospitalar desta internação, será realizado contato telefônico pela equipe de pesquisa para verificar se você teve alguma nova intercorrência neste período como, por exemplo, problemas de saúde, visita à emergência, nova internação hospitalar.

Este estudo será apenas de revisão de registros em prontuários e acompanhamento, não havendo nenhuma interferência no tratamento clínico ou

cirúrgico indicado pela equipe assistencial, que será o mesmo independentemente de você aceitar ou não a participação na pesquisa.

Não são conhecidos riscos pela participação na pesquisa em si, exceto a possibilidade de ocorrer quebra de confidencialidade dos dados. Entretanto os pesquisadores tomarão o cuidado para que isto não ocorra, utilizando sempre um número único para identificação dos participantes, sem a utilização do seu nome.

Não é esperado nenhum benefício direto ao participante, pois não será realizado nenhum tratamento adicional. Contudo, esperamos um benefício para os pacientes com infarto agudo do miocárdio, pois com a conclusão deste trabalho poderemos avaliar melhor o perfil dos pacientes e possíveis complicações dos procedimentos envolvidos. As informações obtidas podem servir para aprimorar o atendimento futuro de pacientes que procuram o serviço de emergência por dor torácica.

Sua participação na pesquisa é totalmente voluntária, ou seja, não é obrigatória. Caso você decida não participar, ou ainda, desistir de participar e retirar seu consentimento, não haverá nenhum prejuízo ao atendimento que você recebe ou possa vir a receber na instituição.

Não está previsto nenhum tipo de pagamento pela sua participação na pesquisa e você não terá nenhum custo com respeito aos procedimentos envolvidos.

Os dados coletados durante a pesquisa serão sempre tratados confidencialmente. Os resultados serão apresentados de forma conjunta, sem a identificação dos participantes, ou seja, o seu nome não aparecerá na publicação dos resultados.

Caso você tenha dúvidas, poderá entrar em contato com o pesquisador responsável Marco Vugman Wainstein, pelo telefone 51 33598342, com o pesquisador Felipe Homem Valle, pelo telefone 51 33598342 ou com o Comitê de Ética em Pesquisa

do Hospital de Clínicas de Porto Alegre (HCPA), pelo telefone (51) 33597640, ou no 2º andar do HCPA, sala 2227, de segunda à sexta, das 8h às 17h.

Esse Termo é assinado em duas vias, sendo uma para o participante e outra para os pesquisadores.

_____

Nome do participante da pesquisa

_____

Assinatura

_____

Nome do responsável (se aplicável)

_____

Assinatura

_____

Nome do pesquisador que aplicou o Termo

_____

Assinatura

Local e Data: _____

11. ANEXO II

REGRISTRO IAM ACTP PRIMARIA

1. Paciente:_____

2. Data do Procedimento: ____/____/_____

3. Data Alta ____/____/____

4. Sexo: (M) (F)

5. Idade: _____

6. Cor:_____

7. Telefones: ( )_____

8. Prontuário:_____

9. Número do Exame:_____

10. Procedência:_____

11. Entrada via: (1) E-HCPA (2)SAMU (3)Intra-Hosp (4) Transferência

Quadro Clínico

Primária Território (1) Anterior (2) Inferior (3) Lateral

Tempo dor-porta: _____H_____min Tempo porta-balão:_____min

Tempo lido-balão: _____min Tempo cronômetro-balao: _____min

Tempo de Transferência:_____H_____min

Horário: (1) 08-20 horas (2) 20-24h (3)24-08h

Dia Semana: (1) Segunda a Sexta (2)Sábado ou domingo

Exame Físico

Killip I (1) Killip II (2) Killip III (3) Kilip IV (4)

BAVT (0) Não (1) Sim PCR (0) Não (1) Sim

Necessidade de MP (0) Não (1) Sim BIA (0) Não (1) Sim

PA admissão:_____**/**_____mmHg **- Hipotensão Sistólica <80mmHg** (0) Não (1) Sim

FC admissão:_____**bpm**

Características Clínicas

HAS (0) Não (1) Sim **Insulina** (0) Não (1) Sim

DM (0) Não (1) Sim **Tabaco** (0) Não (1) Sim (2) Ex-Tabagista

Antiplaquetários Uso prévio: AAS: (0) Não (1) Sim Clopidogrel: (0) Não (1) Sim

IAM Prévio (0) Não (1) Sim

AVE Prévio (0) Não (1) Sim **DPOC:** (0) Não (1) Sim

ICC conhecido (0) Não (1) Sim

IRC conhecida (DCE< 60) (0) Não (1) Sim **Dialítica** (0) Não (1) Sim

DVP (0)Não (1) Sim

TIMI SCORE

- Idade > 75 (3)
- Idade 65-74 (2)
- DM/HAS OU Angina (1)

✓ PAS < 100mmHg (3)

✓ FC>100 bpm (2)

✓ Killip II, III ou IV (2)

✓ Peso < 67kg (1)

❖ Delta T até reperfusão >4horas (1)

❖ Supra de ST na parede Anterior ou BRE de 3º Grau (1)

TOTAL(0-14):_____

Avaliação Laboratorial Basal Pré Procedimento

Creatinina _____mg/dL **MDRD (caso <60): _____CKD-EPI_____**

Creatinina **Pós Procedimento**: _____mg/dL

NIC (0) Não (1) Sim ( )Sem Cr controle [>0,5mg/dL ou >25%]

Troponinas admissão: _____ng/mL Troponinas Pico_____ng/mL Potássio _____mEq/

Plaquetas_____ **x10³/µL VPM**: _____fl

Hemoglobina _____g/dL Hematócrito: _____% RDW:_____% Leucócitos Totais_____

x10³/µL Neut. Segmentados: _____x10³/µL Bastões _____ x10³/µL

Linfócitos:_____ **x10³/µL**

48-72h após Procedimento

Hemoglobina _____g/dL Hematócrito: _____% RDW:_____% Leucócitos Totais_____ x10³/µL

Neut. Segmentados: _____x10³/µL Bastões _____ x10³/µL Linfócitos:_____ x10³/µL

Função Ventricular Esquerda no Ecocardiograma

Fração Ejeção Quantitativa: _____ % *(Obs. pode ser a média do valor)* ( ) Eco Não Realizado

Peso:_____kg Altura:_____cm

Padrão Coronariano

-Extensão da doença coronária (>70% e > 50% TCE)

(1)Uniarterial (2) Biarterial (3)Triarterial (4)TCE + 1 vaso (5) TCE + 2 vasos (6) TCE+3vasos

Intervenção prévia: (0) Não (1)Sim (2) CRM

Informações Gerais sobre a Intervenção Terapêutica

Via de Acesso: (1) Radial (2)Femoral (3) Conversão **Lado do Acesso:** (1)Direito (2)Esquerdo

Introdutor (1) 05f (2)06 f (3)07f

Características angiográficas/tratamento:

Coronária/enxertos: (1) Coronária nativa (2) MAM-E (3) PVS

Vaso Culpado

(1) ACD (2) ADA (3)ACX (4) TCE (5) Diag ou intermédio (6) MArg (7)DP

(8) Ponte Safena (9) Mamaria (10) Posteriolateral

TIMI Pré (0) (1) (2) (3)

Fluxo após passagem guia 0.014 TIMI (0) (1) (2) (3)

Fluxo pós Aspiração TIMI (0) (1) (2) (3) *(9) Não se aplica*

Tipo de Lesão Tratada: (1) Artéria Nativa (2)Trombose Intrastent

Stent Direto (0) Não (1) Sim

Pós Dilatação (0) Não (1) Sim

Overlapping (se >1 stent) (0) Não (1) Sim *(9) Não se aplica*

Aspiração Trombo (0) Não (1) Sim (2) Aspiração de Resgate

Materiais

Só Balão (0) Não (1) Sim

Stent Farmacológico (0) Não (1) Sim

Stent _____

Diâmetro _____

Comprimento ____

Stent _____	Stent _____
Diâmetro _____mm	Diâmetro _____mm
Comprimento _____	Comprimento _____

Quantidade de Stents utilizados no procedimento _____

Grau de Estenose após Procedimento: _____%

Timi Pós (0) (1) (2) (3)

Sucesso Angiográfico Final (1)Sucesso (0)Insucesso

Medicações Administradas durante Procedimento

( )AAS

( )Clopidogrel

( )Heparina não Fracionada

( )Heparina de baixo peso molecular

( )Abciximab

( )Ticagrelor

Contraste volume: _____ml

Complicações alérgicas graves (anfilactoides ou anafiláticas (0) Não (1) Sim

Dose de Radiação_____

Tempo de Escolpa:_____

Complicações Durante o Procedimento

(0) Não (1) no reflow (2) embolização distal (3) re-oclusão (4) perfuração (5)óbito (6) Oclusão de Ramo

(7) Estenose Residual

Lesão Grave Não culpada

(1) Da (2) CD (3) CX (4) DG (5) MG (6) TCE (7) DP

TTO ad hoc (0) Não (1) Sim

(1)ACTP Vaso (1) Da (2) CD (3) CX (4) DG (5) MG (6) TCE (7) DP

Mesma internação? (0) Não (1) Sim [se *Adhoc* = (1), *mesma internação* = (1)]

(2)CRM

(3)Tratamento clínico

Número Total de Vasos Tratados: _____

Syntax Score: **(99)** CRM prévia **(999)** Filme Não Disponível

Clínical Syntax: **(99)**CRM prévia **(999)** Sem Eco

SEGUIMENTO HOSPITALAR

Complicações vasculares antes da alta hospitalar

(0) Não (1) Hematoma >5cm (2) Fístula AV (3) Pseudo Aneurimas (4) Hematoma retroperitoneal

(5) perfuração radial

Transfusão durante a internação: (0) Não (1) Sim

Complicações antes alta:

Óbito (0) Não (1) Sim

Se óbito durante ACTP (0) Não (1) Sim

Novo IAM (0) Não (1) Sim

AVE (0) Não (1) Sim

Trombose Stent (0) Não (1) Sim

Seguimento Por contato telefônico 30 dias

Realizado ( ) Sim ( ) Não

Bolsista: _____

Complicações

1.Depois da alta do HCPA, o Sr teve alguma nova internação hospitalar? Baixou hospital de novo?

( ) Sim ( ) Não

Qual Hospital?

Foi feito novo cateterismo cardíaco?

Foi colocado stent?

2.Teve alguma visita à a emergência? **( ) Sim ( ) Não ( ) NSA**

Quando? Qual Hospital?

3. Foi feito diagnóstico de novo infarto ? ( ) Sim ( ) Não ( ) NSA

4. Depois da alta do HCPA, teve algum problema sério de saúde como derrame, AVE, isquemia cerebral? ( ) Sim ( ) Não ( ) NSA

Quando? Qual Hospital?

5. Depois da alta do HCPA, vem sentido dor no peito, angina?

( ) Sim ( ) Não ( ) NSA Classe (I) (II) (III) (IV)

6. Depois da alta do HCPA, vem sentindo falta de ar ou cansaço?

( ) Sim ( ) Não ( ) NSA NYHA Casse (I) (II) (III) (IV)

IMPRESSÃO (BANCO)

Óbito (0) Não (1) Sim

Novo IAM (0) Não (1) Sim

AVE (0) Não (1) Sim

Trombose Stent (0) Não (1) Sim

Revasc Lesão ou vaso alvo (0) Não (1) Sim

Angina Classe 3 ou classe 4 (0) Não (1) Sim

Reinternação por ICC (0) Não (1) Sim

Medicação Alta

- AAS (0) Não (1) Sim
- Clopidogrel (0) Não (1) Sim
- IECA – Enalapril - (0) Não (1) Sim
- Estatina (0) Não (1) Sim
- BetaBloq – Metoprolol - (0) Não (1) Sim
- Outro AntiPlaq – Ticagrelor (0) Não (1) Sim
- BRA – losartana - (0) Não (1) Sim
- Antagonista Aldosterona - Espironolactona - (0) Não (1) Sim
- Digitálico (0) Não (1) Sim
- AntiCoagulante – warfarina (0) Não (1) Sim

Antagonista Canal de Ca (0) Não (1) Sim

Verapamil/ diltiazem /anlodipno.