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Bigdata e tele-eletrocardiografia: um estudo com a coorte eletrônica dos eletrocardiogramas da Rede de Teleassistência de Minas Gerais

Universidade Federal de Minas Gerais
Faculdade de Medicina
Programa de Pós-Graduação em Infectologia e Medicina Tropical
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Tese apresentada ao Programa de Pós-Graduação em Ciências da Saúde: Infectologia e Medicina Tropical da Faculdade de Medicina da Universidade Federal de Minas Gerais na linha de pesquisa de Telessaúde, como requisito parcial para a obtenção do título de Doutor.

Orientador: Prof. Dr. Antonio Luiz Pinho Ribeiro

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ATA DE DEFESA DE TESE

Às **14:00** horas do dia 18 de agosto de 2021, por videoconferência pela plataforma ZOOM, realizou-se a sessão pública para a 199ª defesa de tese de **GABRIELA MIANA DE MATTOS PAIXÃO**, número de registro 2018712726, graduada no curso de MEDICINA, como requisito parcial para a obtenção do grau de Doutor em CIÊNCIAS DA SAÚDE. A presidência da sessão coube ao professor **ANTONIO LUIZ PINHO RIBEIRO**, orientador. Inicialmente, o presidente fez a apresentação da Comissão Examinadora assim constituída: **PROF. NELSON SAMESIMA (INCOR - HCFMUSP), PROF. EDSON AMARO JUNIOR (HOSPITAL ISRAELITA ALBERT EINSTEIN), PROFA. GRAZIELA CHEQUER (UFMG), PROFA. CARLA JORGE MACHADO (UFMG), PROF. ANTONIO LUIZ PINHO RIBEIRO - ORIENTADOR (UFMG)**. Em seguida, a candidata fez a apresentação do trabalho que constitui sua **Tese de Doutorado**, intitulada: ***"Bigdata e tele-eletrocardiografia: um estudo com a coorte eletrônica dos eletrocardiogramas da Rede de Teleassistência de Minas Gerais".*** Seguiu-se a arguição pelos examinadores e logo após, a Comissão reuniu-se, sem a presença da candidata e do público e decidiu considerar **APROVADA** a **Tese de Doutorado**. O resultado final foi comunicado publicamente a candidata pelo presidente da Comissão. Nada mais havendo a tratar, o presidente encerrou a sessão e lavrou a presente ata que, depois de lida, se aprovada, será assinada pela Comissão Examinadora.

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Para meus pais, Ricardo e Lúcia,
Meus exemplos.

Para Lucas e Joaquim,meus amores e incentivadores.

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RESUMO

Introdução: As doenças cardiovasculares são as principais causas de mortalidade no Brasil e no mundo. O eletrocardiograma (ECG) é um exame de baixo custo, fácil acesso e não invasivo que faz parte da avaliação inicial do paciente na investigação de cardiopatia, bem como do seguimento clínico dos pacientes sabidamente portadores de doenças cardiovasculares. A identificação de novas variáveis eletrocardiográficas como fatores de risco para eventos cardiovasculares é um importante objetivo de pesquisa dentre as coortes eletrônicas. Na eletrocardiografia, os algoritmos de *machine learning* (ML) têm sido bastante estudados tanto para o diagnóstico automático de alterações eletrocardiográficas, bem como para a predição de eventos cardiovasculares e identificação de novos fatores de risco cardiovasculares.

Objetivos: Avaliar a presença de alterações maiores de Minnesota pelo ECG como fator de risco independente para mortalidade e o impacto prognóstico da idade eletrocardiográfica predita por técnicas de ML.

Métodos: Trata-se de estudo observacional retrospectivo que avaliou pacientes que realizaram eletrocardiograma digital pela Rede de Teleassistência de Minas Gerais de 2010 a 2017. Realizou-se pareamento probabilístico entre os dados do ECG e o sistema de informação de mortalidade do estado de Minas Gerais. Dados clínicos auto-relatados foram utlizados. Os ECGs foram laudados por cardiologistas treinados e, também, interpretados pelos *softwares* automáticos de *Glasgow* e *Minnesota*. Uma rede neural convolucional foi treinada para predizer a idade baseada no ECG de 12 derivações.

Resultados: 1.558.421 pacientes acima de 16 anos foram incluídos no estudo. As anormalidades eletrocardiográficas avaliadas foram: bloqueio atrioventricular (BAV), bloqueio de ramo direito (BRD), bloqueio de ramo esquerdo (BRE) e pré- excitação ventricular. Em um seguimento médio de 3,7 anos, a presença de BRE, BRD e BAV foram associadas, independemente, a maior mortalidade (p< 0,001). Pacientes com pré-excitação ventricular não apresentaram maior risco de morte (p=0,47). Pacientes com ECG com idade superior a 8 anos que a cronológica apresentaram maior risco de morte (razão de risco (HR) 1,79, p <0,001), enquanto aqueles com ECG com idade inferior a 8 anos que a cronológica apresentaram menor risco (HR 0,78, p <0,001).

Conclusões: Coortes eletrônicas podem auxiliar a determinar o valor prognóstico das anormalidades eletrocardiográficas. A idade eletrocardiográfica predita por ML pode adicionar informações prognósticas à interpretação convencional do ECG.

Palavras-chave: coorte eletrônica, eletrocardiograma, *machine learning*, mortalidade.

ABSTRACT

Introduction: Cardiovascular diseases are the main causes of mortality in Brazil and worldwide. The electrocardiogram (ECG) is a low-cost, easy to access and non-invasive test that is part of the initial assessment of the patient in the investigation of heart disease, as well as the clinical follow-up. The identification of new electrocardiographic variables as risk factors for cardiovascular events is an important objective of research among electronic cohorts. In electrocardiography, machine learning (ML) algorithms have been extensively studied both for the automatic diagnosis of electrocardiographic changes, as well as for the prediction of cardiovascular events and the identification of new cardiovascular risk factors.

Objective: To evaluate the presence of major ECG abnormalities as an independent risk factor for mortality and the prognostic impact of electrocardiographic age predicted by ML techniques.

Methods: This is an observational retrospective study. Patients who performed digital electrocardiograms by Telehealth Network of Minas Gerais from 2010 to 2017 were assessed. A probabilistic linkage between data from the national mortality information system and our ECG database was made. Clinical data were self-reported, and ECGs were interpreted by a team of trained cardiologists and by automatic software (Glasgow and Minnesota). A deep convolutional neural network was trained to predict a patient's age from the 12-lead ECG.

Results: 1,558,421 patients over 16 years old were included in the study. The electrocardiographic abnormalities assessed were: atrioventricular block (ABV), right bundle branch block (RBBB), left bundle branch block (LBBB) and ventricular pre-excitation. In an average follow-up of 3.7 years, the presence of AVB, RBBB and LBBB was independently associated with higher mortality ($p < 0.001$). Patients with ventricular pre-excitation were not at higher risk of death ($p = 0.47$). Patients with ECG-age more than 8 years greater than chronological age had a higher mortality rate (hazard ratio (HR) 1.79, $p<0.001$), whereas those with ECG-age more than 8 years less than chronological age had a lower mortality rate (HR 0.78, $p<0.001$).

Conclusions: Electronic cohorts can help to determine the prognostic value of electrocardiographic abnormalities. ML-enabled analysis of the ECG can add prognostic information to the interpretation of the 12-lead ECGs.

Key words: electronic cohort, electrocardiogram, machine learning, mortality.

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LISTA DE ABREVIATURAS E SIGLAS

AV	Atrioventricular
AUC	Área sobre a curva
BAV	Bloqueio atrioventricular
BRD	Bloqueio de ramo direito
BRE	Bloqueio de ramo esquerdo
CID10	Código Internacional de Doenças
CODE	*Clinical Outcomes in Digital Electrocardiography*
ECG	Eletrocardiograma
EEF	Estudo eletrofisiológico
ELSA-Brasil	Estudo Longitudinal de Saúde do Adulto
FA	Fibrilação atrial
FAPEMIG	Fundação de Amparo à Pesquisa de Minas Gerais
FRIL	*Fine-grained record linkage software*
IA	Inteligência artificial
IC	Intervalo de confiança
LAC	*Lazy Associative Classifier*
ML	*Machine-learning*
MSC	Morte súbita cardíaca
RNA	Rede neural artificial
ROC	*Receiver Operating Characteristic*
RTMG	Rede de Teleassistência de Minas Gerais
SaMi-Trop	São Paulo-Minas Gerais *Tropical Medicine Research Center*
SIH	Sistema de Informação de Hospitalização
SIM	Sistema de Informação de Mortalidade
SVM	*Support Vector Machine*
SVR	Regressão do vetor de suporte
VPP	Valor preditivo positivo
VPN	Valor preditivo negativo
WPW	*Wolf-Parkinson-White*

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1. CONSIDERAÇÕES INICIAIS

O Centro de Telessaúde do Hospital das Clínicas da Universidade Federal de Minas Gerais foi criado em 2005(1), sendo implementada a rede de tele-eletrocardiografia em 2006, priorizando os municípios remotos do estado, distantes de grandes centros, com baixo índice de desenvolvimento humano e com pequena população.

O advento do programa de tele eletrocardiografia possibilitou a expansão do serviço para vários municípios de Minas Gerais com novos convênios com a Secretaria do Estado da Saúde de Minas Gerais. Em 2010, a Rede de Teleassistência de Minas Gerais (RTMG) foi registrada na Fundação de Amparo à Pesquisa de Minas Gerais (FAPEMIG) como uma das redes de pesquisa de Minas Gerais.

A RTMG, atualmente, abrange 817 dos 853 municípios de Minas Gerais além de 124 municípios na Bahia, 70 no Mato Grosso, 30 no Ceará, 12 no Acre, 7 em Roraima, 3 em Pernambuco e 1 no Maranhão e Tocantins. Desde a sua implementação, a RTMG realizou mais de cinco milhões de eletrocardiogramas (ECG) laudados por equipe especializada.

Diante desse enorme banco de dados de ECG, surgiu o projeto CODE (´´*Clinical Outcomes in Digital Electrocardiography*´´)(2) idealizado pelo Prof. Antonio Luiz Pinho Ribeiro. O projeto de pesquisa tem como objetivo correlacionar as alterações eletrocardiográficas com desfechos de mortalidade geral e cardiovascular e de internações hospitalares por causas cardiovasculares. O CODE possui uma equipe multiprofissional composta de médicos cardiologistas, estatísticos, engenheiros eletricistas e cientistas da computação. O grupo se reúne regularmente desde o início de 2017.

Minha participação no projeto ocorreu desde o seu início, em janeiro de 2017, quando retornei da residência médica em São Paulo. Havia feito contato com o Prof. Tom para início da minha pós-graduação. Ele me apresentou a sua ideia e começamos a nos organizar para efetuá-la. Fui responsável pela redação do projeto de pesquisa, bem como a sua submissão ao Comitê de Ética em Pesquisa. Realizamos parcerias com a Secretária de Saúde de Belo Horizonte e de Minas Gerais para a disponibilização das bases de dados do Sistema de Informação de Mortalidade (SIM) e de Internação Hospitalar (SIH) para o pareamento com a base de dados dos ECG.

Os ECG, entre 2006 e 2017, eram laudados em forma de texto-livre pelos cardiologistas. Dessa forma, foi necessário o uso da inteligência artificial (IA) para extrair as classes diagnósticas de anormalidades eletrocardiográficas, padronizadas como classes ¯CODE‖, dos laudos eletrocardiográficos de texto livre. Mais de 30.000 ECG foram revisados manualmente sob a minha coordenação. Paralelamente, um novo sistema de laudos de ECG da RTMG estava em desenvolvimento e foi implantado no início de 2018. O novo sistema possibilitou uma padronização no laudo, com base nas classes ¯CODE‖, além da incorporação do sistema de medidas automáticas da Universidade de Glasgow para o auxílio no laudo médico.

A base de dados eletrocardiográficas da RTMG foi pareada com os dados do SIM de Minas Gerais em 2017 e, mais recentemente, em 2020, com os dados do SIH de Belo Horizonte. O pareamento probabilístico foi realizado por um dos integrantes da equipe do CODE e eu fui responsável pela validação dos resultados do pareamento.

Atualmente, o grupo expandiu e também trabalha em projetos de eletrocardiografia com ´´*machine-learning*´´, desenvolvimento de ferramentas automáticas para o reconhecimento de ruído e segmentação do traçado eletrocardiográfico.

Para a tese de doutorado em questão, utilizamos uma parte do banco de dados do CODE, com objetivo de avaliar a associação entre alterações maiores eletrocardiográficas(3) com a mortalidade geral e cardiovascular (artigos 1,2 e 3). Além disso, analisamos a idade eletrocardiográfica estimada pela IA como preditor de mortalidade (artigo 4). A tese se vincula à linha de pesquisa em ´´Telessaúde´´, com objetivos comuns de melhoria da assistência à saúde e da qualidade de vida da população de Minas Gerais.

2. INTRODUÇÃO

As doenças cardiovasculares são as principais causas de mortalidade no Brasil e no mundo(4). O ECG é um exame de baixo custo, fácil acesso e não invasivo que faz parte da avaliação inicial do paciente na investigação de cardiopatia, bem como do seguimento clínico dos pacientes sabidamente portadores de doenças cardiovasculares.

Os estudos epidemiológicos com o ECG começaram na década de 40, com o surgimento dos estudos cardiovasculares de coorte(5). No entanto, os laudos eletrocardiográficos apresentavam variações significativas, conforme o examinador, devido à falta de padronização(6). Nesse contexto, o código de Minnesota(3) foi criado em 1960, com o objetivo de uniformizar a descrição eletrocardiográfica e possibilitar a comparação entre diferentes populações. O código foi validado em diversos estudos, inclusive para o uso no ECG digital(7), e se tornou o método de escolha para a avaliação eletrocardiográfica em estudos epidemiológicos(8).

Estudos populacionais com o uso de ECG começaram a ser publicados, demonstrando o valor prognóstico de anormalidades eletrocardiográficas na predição de eventos cardiovasculares(9)(10). Uma análise agregada dos dados de oito estudos populacionais, publicada em 1978, envolveu um total de 8.390 indivíduos do sexo masculino, com seguimento médio de oito anos(11). Esse estudo confirmou a importância das anormalidades maiores de ECG como preditores de eventos cardíacos(11) (10). Posteriormente, outros estudos populacionais confirmaram o valor prognóstico das alterações eletrocardiográficas, incluindo alterações classificadas como menores(12)(13)(14)(15).

O desenvolvimento do ECG computadorizado(16), associado aos sistemas capazes de transmitir os traçados eletrocardiográficos pela internet e pacotes de software que possibilitam análise e codificação automática dos traçados, revolucionaram a

eletrocardiografia dos estudos populacionais(17). Simultaneamente, a digitalização dos prontuários médicos no sistema de saúde facilitou o surgimento de vários estudos de coortes eletrônicas em eletrocardiografia, com enfoques distintos: desde estudos de prevalência à identificação de fatores prognósticos(18)(19)(20)(21).

A identificação de novas variáveis eletrocardiográficas como fatores de risco para eventos cardiovasculares é um importante objeto de pesquisa dentre as coortes eletrônicas, principalmente quando a indicação da realização de ECG para rastreamento populacional permanece controversa(22)(23) e o beneficio da associação do ECG aos escores tradicionais de risco cardiovascular para discriminação e reclassificação é questionável(22). O uso de parâmetros tradicionais do ECG, como: frequência cardíaca; eixo da onda p, complexo QRS e onda T; intervalo PR; duração da onda p e complexo QRS e intervalo QT, impactam pouco na reclassificação do risco cardiovascular quando adicionados ao escore de Framingham(24). O reconhecimento de potenciais fatores de risco eletrocardiográficos não tradicionais é desejável e o uso de novas tecnologias, como a IA, torna-se método promissor nessa busca.

A IA é uma área da computação que desenvolve mecanismos e dispositivos tecnológicos que simulam o raciocínio humano. É uma ferramenta importante na análise de um grande volume de dados (¯*big data")*(25), principalmente quando há limitação no uso dos métodos estatísticos convencionais. O aprendizado de máquina (em inglês, *machine learning*), ramo da IA, consiste na construção de modelos analíticos automáticos a partir de algoritmos que relacionam grandes bancos de dados informatizados à ciência computacional disponível(26). As técnicas de *machine learning* (ML) são aplicadas em diversas áreas da medicina, como ferramenta de auxílio para avaliação diagnóstica e prognóstica(26).

Na eletrocardiografia, os algoritmos de ML têm sido bastante estudados tanto para o diagnóstico automático de alterações eletrocardiográficas, bem como para a predição

de eventos cardiovasculares e identificação de novos fatores de risco cardiovasculares(27). O diagnóstico automático de algumas anormalidades eletrocardiográficas por técnicas de ML já foi avaliado com bom desempenho, em relação a softwares automáticos de análise e laudos de médicos não especialistas(28),inclusive em cenários de emergências cardiovasculares(29).

Na avaliação prognóstica, os algoritmos de ML foram capazes de predizer fibrilação atrial em pacientes com ritmo sinusal(30). A predição de idade e sexo somente pelo traçado eletrocardiográfico também já foi demonstrada(31). Além disso, a análise isolada do ECG de 12 derivações pode predizer mortalidade em um ano com boa acurácia, mesmo em traçados laudados como normais(32). A IA pode extrair informações do eletrocardiograma que não são valorizadas e/ou desconhecidas pelos métodos convencionais de análise, agregando valor diagnóstico e prognóstico.

No Brasil, existem poucos grandes estudos populacionais, seja por métodos convencionais ou por IA, que objetivam a avaliação de prognóstico cardiovascular. Apesar de serviços sólidos e bem desenvolvidos de telecardiologia, há várias limitações para a obtenção de coortes populacionais eletrônicas, como: implementação incompleta do prontuário eletrônico nos centros de atenção primária e secundária, falta de integração da rede de prontuários com os sistemas de informações e ausência de interface entre os sistemas de informação ambulatorial, hospitalar e de mortalidade. Além disso, a saúde suplementar que atende a 25% da população em Minas Gerais não é contemplada nos sistemas de dados ambulatoriais e hospitalares(33).

Outros fatores que impactam para a realização dos estudos populacionais são: o preenchimento inadequado de declarações de óbito e a colocação errônea dos Códigos Internacionais de Doenças (CID-10). No entanto, para amenizar este problema, o SIM recodifica os chamados códigos *"garbage"* das declarações de óbito, após investigação de prontuários hospitalares, de atendimentos ambulatoriais e/ou abordagem de familiar.

A real prevalência e o impacto prognóstico das alterações maiores eletrocardiográficas na população brasileira ainda persistem como objeto de estudo, devido à escassez de publicações nacionais de coortes populacionais. A extrapolação das informações de estudos de outros centros populacionais, principalmente de países desenvolvidos, não, necessariamente, corresponde à nossa realidade.

O crescente desenvolvimento tecnológico, digitalização das bases de dados e a recente disponibilização da IA impulsionaram centros de referência em pesquisa no Brasil, como a RTMG, a investir ainda mais em estudos populacionais com grande volume de dados. A obtenção da maior quantidade possível de informação clinica e epidemiologicamente significativa de um exame simples, de baixo custo e acessível, como o ECG, possibilita ações para a melhoria na assistência à saúde nos âmbitos individual e coletivo.

3. REVISÃO DA LITERATURA

3.1. ELETROCARDIOGRAFIA

O uso do ECG como ferramenta anual para rastreamento de doenças cardiovasculares na população geral permanece controverso(22)(34)(35). Apesar de ser um exame de baixo custo e acessível, as diretrizes americanas não recomendam sua realização rotineira em pacientes de baixo risco cardiovascular(22). No entanto, a presença ou o desenvolvimento de alterações eletrocardiográficas menores e maiores são preditores de risco para eventos cardiovasculares e mortalidade(35)(36).

O código de Minnesota divide as alterações eletrocardiográficas em maiores e menores(3), conforme o seu impacto prognóstico(15). As alterações maiores representam códigos de ondas Q maiores (1.1 e 1.2), depressão do segmento ST (4.1 e 4.1), inversão de onda T (5.1 e 5.2), bloqueios atrioventriculares (BAV) avançados (6.1 e 6.1), bloqueios completos de ramo esquerdo (BRE), direito (BRD) e inespecífico (7.1, 7.2 e 7.4) e, finalmente, arritmias significativas como extrassístoles ventriculares e fibrilação atrial (FA) ou flutter (8.1 e 8.3 respectivamente). A tabela 1 resume as alterações eletrocardiográficas consideradas maiores e que foram revisadas pelo estudo CODE com seus respectivos códigos de Minnesota. A FA foi objeto de estudo da minha dissertação de mestrado(37) e não será abordada nessa tese.

Tabela 1. Alterações eletrocardiográficas maiores e sua correlação com o Código de Minnesota

Alterações	Código de Minnesota
Bloqueio de ramo esquerdo	7-1
Bloqueio de ramo direito	7-2
Bloqueio intraventricular inespecífico	7-4
Bloqueio de ramo direito + bloqueio divisional anterossuperior esquerdo	7-8
Fibrilação atrial ou Flutter	8-3
Bloqueio atrioventricular de terceiro grau	6-1
Bloqueio atrioventricular de segundo grau	6-2
Bloqueio atrioventricular de primeiro grau	6-3
Padrão de pré-excitação ventricular	6-4

3.1.1. BLOQUEIOS DE RAMO

Os bloqueios de ramo são definidos por duração do intervalo QRS maior ou igual a 120 milisegundos(38). Esse prolongamento do intervalo QRS causa dessincronia elétrica e está associado a pior prognóstico(39),especialmente na insuficiência cardíaca(40).

A prevalência dos bloqueios de ramo varia de 0.9 a 11.5%, dependendo do tipo do bloqueio, da população estudada e das comorbidades associadas (41)(42). O envelhecimento da população, sexo masculino e a presença de doença de Chagas, em nosso meio, estão relacionados com uma maior prevalência(41)(43).

O BRE é um marcador eletrocardiográfico bem estabelecido de doença cardíaca e de pior prognóstico. Em paciente portadores de doença arterial coronariana e insuficiência cardíaca de fração de ejeção reduzida ou preservada, está relacionado a maior morbimortalidade(44)(45). Inclusive na população geral, há maior risco de mortalidade cardiovascular e por todas as causas(42).

Em relação ao BRD, a literatura é controversa. Em indivíduos saudáveis assintomáticos, o prognóstico é considerado benigno(46). No entanto, uma coorte populacional dinamarquesa encontrou associação com maior risco de mortalidade por todas as causas e cardiovascular(47). Para os pacientes cardiopatas com doença arterial coronária e insuficiência cardíaca, o significado prognóstico do BRD também possui resultados conflitantes(42)(48).

3.1.2. BLOQUEIOS ATRIOVENTRICULARES

O nó atrioventricular (AV) é responsável pela conexão elétrica entre os átrios e os ventrículos. O intervalo PR consiste no período desde a despolarização atrial (onda P) até o início da despolarização ventricular (complexo QRS), representando a condução AV(49). O BAV é definido pelo retardo ou pela interrupção da condução AV e pode ser dividido em três graus, conforme sua apresentação eletrocardiográfica(50). Dentre as causas de BAV, podemos citar a cardiopatia isquêmica, a doença degenerativa do sistema de condução, a doença de Chagas, a cardiopatia congênita, as doenças do tecido conjuntivo, as doenças inflamatórias, o uso de medicamentos e o aumento do tônus vagal (51).

Sua prevalência varia de 0,6% a 6,04% na literatura, dependendo da população estudada e do grau do BAV(41)(52). É mais frequente em idosos e homens(41), sendo o BAV de primeiro grau o mais comum(51).

O BAV de primeiro grau era considerado benigno na população geral, baseado em estudos longitudinais com homens jovens e de meia idade da década de 80(53)(54)(55). No entanto, coorte populacional de Framingham com maior tempo de seguimento clínico evidenciou o contrário(51). BAV de primeiro grau está associado a maior risco de

fibrilação atrial, acidente vascular cerebral, implante de marcapasso, hospitalização por insuficiência cardíaca e morte(51)(56)(57).

Os BAV de segundo grau possuem prognóstico variado, conforme o seu subtipo. O BAV do tipo Mobitz I é usualmente benigno, principalmente em pacientes jovens sem doença cardíaca estrutural(58) em que o tônus vagal é aumentado e não há lesão anatômica no sistema de condução(59). Os pacientes mais idosos podem evoluir com a necessidade de implante de marcapasso(60). A evolução dos casos de BAV 2:1 depende do local do bloqueio: nodal ou infranodal(50).

Os BAV de segundo grau Mobitz II, avançado e de terceiro grau adquirido constituem indicações de implante de marcapasso definitivo, mesmo em pacientes assintomáticos, na ausência de causas reversíveis(50). Há maior morbimortalidade nesses casos devido a maior comprometimento do sistema de condução elétrica e a maior associação com doenças cardiovasculares(50).

3.1.3. PRÉ-EXCITAÇÃO VENTRICULAR

A pré-excitação ventricular ocorre devido à presença de uma ou mais vias acessórias de condução atrioventricular, que se manifestam no ECG por um intervalo PR curto, onda delta e aumento do complexo QRS(38). A prevalência varia entre 0,1 a 0,3%(61). O padrão do ECG associado a palpitações ou síncope estabelece o diagnóstico da síndrome de Wolf-Parkinson-White (WPW).

Nos pacientes sintomáticos, ou seja, portadores da síndrome de WPW, a ocorrência de arritmia ventricular é maior, com risco estimado de morte súbita cardíaca (MSC) de 0,25% ao ano ou 3% a 4% no decorrer da vida(62). Nesses casos, a indicação do estudo eletrofisiológico (EEF) com ablação por cateter da via acessória está bem estabelecida e é recomendação classe I, nível de evidência A nas diretrizes internacionais(63).

A história natural da pré-excitação ventricular nos pacientes assintomáticos não é bem elucidada(64). As evidências científicas para a estratificação de risco invasiva de MSC com EEF de forma indiscriminada são limitadas(65). Os estudos randomizados realizados possuiam amostra pequena(66), com grande parte da população oriunda de hospitais terciários(67).

Coortes das décadas de 50 e 60 com um número pequeno de pacientes evidenciaram uma evolução favorável para os portadores de pré-excitação ventricular(62)(68). Recentemente, um estudo populacional dinamarquês com mais de 300.000 pacientes da atenção primária à saúde não demonstrou associação entre mortalidade e pré-excitação ventricular. No entanto, houve um maior risco de desenvolvimento de fibrilação atrial e insuficiência cardíaca. Em subanálise de pacientes maiores de 65 anos, o risco de morte foi maior(64).

3.2. MACHINE LEARNING

Artigo de revisão aceito para publicação em 02/12/2020 na revista Arquivos Brasileiros de Cardiologia

Machine Learning na medicina: revisão e aplicabilidade

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Resumo:

O uso de Inteligência Artificial (IA) na Medicina é uma realidade desde a virada do século, com progressivo aprimoramento das suas técnicas. O aprendizado de máquina (em inglês, machine learning) é uma forma de inteligência artificial que busca uma interseção de técnicas matemáticas e estatísticas com algoritmos computacionais. O aprendizado de máquina (em inglês, machine learning) consiste na construção de modelos analíticos automáticos a partir de algoritmos que relacionam grandes bancos de dados informatizados à ciência computacional disponível. As técnicas de machine learning (ML) são aplicadas em diversas áreas da medicina desde o desenvolvimento de pesquisa científica à ferramenta de auxílio para avaliação diagnóstica e prognóstica. Na cardiologia, ML tem sido amplamente pesquisada na propedêutica cardiovascular, principalmente na ecocardiografia e eletrocardiografia, com resultados promissores. Como método adjuvante na predição de eventos cardíacos adversos, ML também obteve bons resultados iniciais em comparação aos métodos tradicionais. Futuramente, a incorporação dos componentes genômicos aos escores de risco já estabelecidos pode contribuir na estimativa do risco de doenças cardiovasculares. O conhecimento das técnicas de ML com suas aplicabilidades clínicas bem como limitações é importante para a melhoria da prática médica moderna e individualizada.

Descritores: *machine learning*, medicina, cardiologia

3.2.1. INTRODUÇÃO

O aprendizado de máquina, ou *Machine Learning* (ML), é um ramo da Inteligência Artificial que explora o estudo e a construção de algoritmos computacionais a partir do aprendizado por dados[1,2], ao invés de instruções pré-programadas[3]. O objetivo principal de um modelo de ML é construir um sistema de computador que aprenda com um banco

de dados pré-definidos e gere, ao final, um modelo de predição, classificação ou detecção.

A aplicação de ML na prática é voltada principalmente para o manuseio de bases de dados consolidadas com informações heterogêneas em que há uma limitação do uso das técnicas de estatística convencionais[4,5]. Os algoritmos de ML já estão difundidos em diversas áreas, como: sistemas bancários para detecção de fraudes, mecanismos de busca na internet, sistemas de vigilância em vídeo, segurança de dados, logística de empresas, robótica e, na medicina, para diagnóstico e prognóstico[6]. Com a digitalização dos prontuários médicos, exames laboratoriais e de imagem, houve um crescimento dos bancos de dados que são fontes para a aplicação de técnicas de ML, visando a prevenção, diagnóstico precoce e o tratamento das doenças.

Este artigo de revisão aborda uma introdução sobre ML dividida em: definição, modelos de aprendizagem e técnicas; seguida de uma revisão sistemática de artigos sobre a sua aplicabilidade na Medicina e, principalmente, na Cardiologia. O objetivo é apresentar ML para médicos e profissionais de saúde como uma ferramenta de auxílio para a prática clínica.

Para a estruturação deste artigo de revisão foram pesquisadas nas duas bases de dados: *PubMed(NCBI)* e *Medline* os seguintes descritores na língua inglesa: "*machine learning*", "*artificial intelligence*", "*unsupervised learning*", "*supervised learning*"e "*neural networks*" e "*cardiology*". Foram incluídos estudos prospectivos e retrospectivos e excluídos casos clínicos e resumos apresentados em congressos (não publicados sob a forma de artigo). A elegibilidade de cada estudo foi avaliada por dois investigadores. As opiniões divergentes relativamente à relevância dos artigos foram abordadas por consenso entre os autores.

3.2.2. MACHINE LEARNING

O aprendizado de máquina é um subcampo da Ciência da Computação que busca uma interseção de técnicas matemáticas e estatísticas com algoritmos computacionais, visando extrair informações ou padrões contidos em um conjunto de dados para a construção de modelos matemáticos estatísticos[3,7]. Utiliza algoritmos com o conceito de inteligência artificial e é aplicada em determinadas situações em que se busca padrões em um conjunto de variáveis com o intuito de prever um resultado específico de interesse[8,9].

A maioria das técnicas convencionais usadas em sistemas computacionais aplicados à medicina empregam o conceito de algoritmos baseados em regras, chamados de ―sistemas especialistas‖. Assim, o desenvolvedor codifica os conhecimentos médicos sobre um determinado assunto para esses sistemas, utilizando regras já conhecidas. Já as técnicas de ML manuseiam um grande número de variáveis, buscando uma variedade de novas combinações que possam prever um resultado com confiabilidade, muitas vezes, buscando solucionar problemas complexos, tais como big data[7].

Doug Laney (2001) definiu um modelo de ―3Vs‖ para conceituar o termo big data: grande volume, alta velocidade e alta variedade de informações que exigem novas técnicas de processamento de forma a permitir descobertas e otimizar processos[10]. O termo big data pode ser tanto um conjunto de dados de tamanho enorme, que nenhuma das ferramentas tradicionais de gerenciamento de dados é capaz de armazená-los ou processá-los com eficiência, como também pode se referir à um tipo de tecnologia (como instalações de armazenamento, ferramentas e processos)[11].

O processo de desenvolvimento de um algoritmo de ML é dividido em três fases: pré-processamento, treinamento e avaliação do modelo (Figura 1). A primeira fase consiste em organizar o banco de dados, definir a pergunta de pesquisa e dividir os dados

em: treinamento e teste. No treinamento, o aprendizado pode ocorrer de forma supervisionada ou não supervisionada[12-15]. O aprendizado supervisionado é baseado no treinamento de uma amostra de dados com a classificação correta já atribuída enquanto o não supervisionado se refere à capacidade de aprender e organizar informações sem a atribuição da classificação correta[14]. Na fase de avaliação, o modelo é comparado com os dados de teste e os resultados são gerados. Portanto, os algoritmos de ML aprendem através de repetidas observações e estabelecem um padrão de mapeamento com o intuito de rotular os dados e criar um modelo que generaliza as informações, de modo que novos dados (jamais analisados pelo algoritmo) possam ser rotulados com precisão e confiabilidade[15].

É importante salientar que o processo de desenvolvimento de um algoritmo de ML deve ser realizado com uma base de dados consolidada e validada, pois modelos de ML desenvolvidos com dados não consolidados podem gerar resultados enganosos[5].

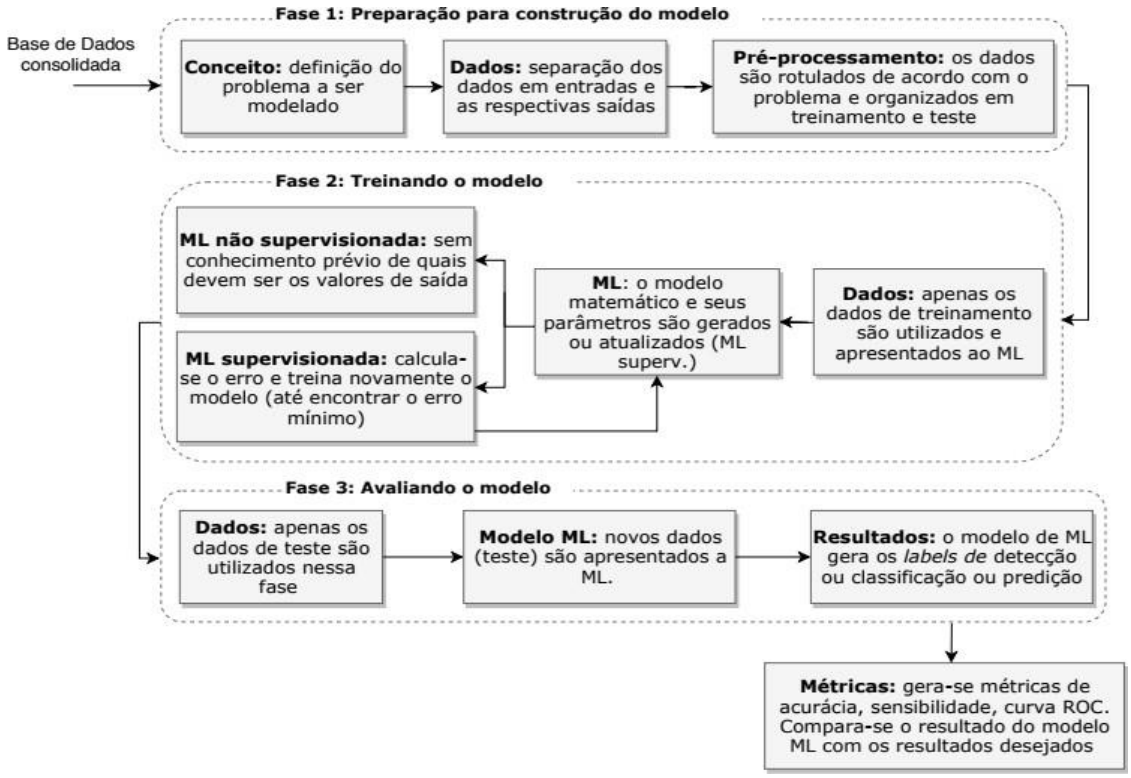

Figura 1. Fases para o desenvolvimento de algoritmos de *Machine Learning*[15]

3.2.2.1. *MACHINE LEARNING* SUPERVISIONADA E NÃO SUPERVISIONADA

A principal diferença entre os modelos de aprendizagem supervisionado e não supervisionado está no algoritmo de treinamento. No aprendizado não supervisionado, o modelo de ML extrai as características dos dados e constrói uma representação sem o conhecimento prévio dos rótulos de cada dado, ou seja, identifica o padrão das informações de classe heuristicamente. Essa falta de supervisão para o algoritmo pode ser vantajosa, pois permite que o algoritmo analise os padrões que não foram considerados anteriormente[12-14] .

No aprendizado supervisionado, o modelo do ML tem o conhecimento do rótulo dos dados, ou seja, as amostras estão corretamente classificadas. O treinamento é baseado na comparação entre o resultado obtido do modelo e o rótulo previamente classificado. Esse processo é repetido até se obter um erro mínimo[14].

A tabela 1 resume as principais características de cada tipo de modelo de aprendizado, bem como suas vantagens e desvantagens e aplicabilidade prática.

Tabela 1. Comparativo entre processo de aprendizagem supervisionado e não supervisionado

	Aprendizado supervisionado	**Aprendizado não supervisionado**
Definição	Algoritmos que aprendem relações entre atributos de entrada e de saída a partir de conjunto de exemplos rotulados	Algoritmos que buscam encontrar padrões em agrupamentos de dados com características semelhantes, em busca de categorias e desfechos ainda não identificados ou não informados
Vantagens	Análise de múltiplos parâmetros; solução rápida e automática para questões de grande escala e elevada acurácia	Menor interferência humana na análise dos dados; excelente para fontes de dados multimodais ou multidimensionais e permite identificação de novos desfechos
Desvantagens	Necessidade dos dados serem rotulados e para grandes volumes de dados pode ser impraticável. Tendência ao sobreajuste dos dados	Custo elevado e técnicas complexas; necessita grande quantidade de dados para elaboração do algoritmo e a interpretação dos resultados pode ser desafiadora
Principais tarefas	Regressão, classificação, modelo prognóstico e análise de sobrevivência	Redução da dimensionalidade do problema e agrupamento
Exemplos de algoritmos	Regressão logística, árvores de decisão, *random forests* e redes neurais artificiais	Análise das componentes principais, agrupamento hierárquico, *autoencoder*s, análise linear de discriminantes

3.2.2.2. TÉCNICAS DE *MACHINE LEARNING*

Diversas técnicas de ML têm sido aplicadas como forma de sistemas de diagnóstico auxiliado por computador, tais como: redes neurais artificiais, regressão logística, árvore de decisão, *random forests*, rede *bayesiana, deep learning,* SVM (Support Vector Machine) e dentre outros[16-21]. Utilizam modelos matemáticos por meio dos dados para aprendizagem e/ou organização das informações[12]. Alguns modelos utilizam representações matemáticas com alto grau de abstração (modelos matemáticos complexos). Neste caso, não é possível decifrar ou interpretar os métodos utilizados para obtenção dos resultados de predição, detecção ou classificação, de modo que tais

modelos de ML são chamados de ¯caixa preta‖[22].

Uma rede neural artificial (RNA) é um modelo computacional e matemático desenvolvido para funcionar como o cérebro humano. Uma RNA possui diversos elementos de interconexões (camada de preditores, camada oculta e camada de resultados) e a relação entre essas camadas é inspirada nas conexões sinápticas entre os neurônios (Figura 2)[12,15,23].

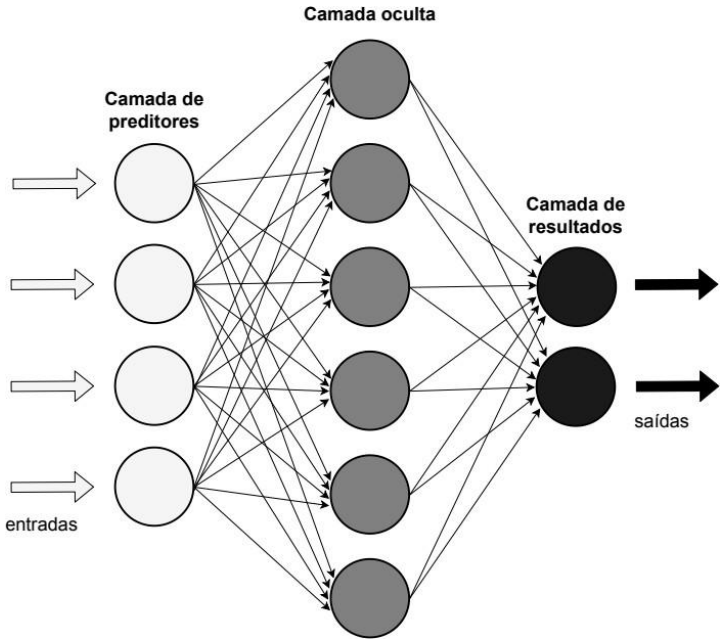

Figura 2. Estrutura do funcionamento de uma rede neural artificial[19]

Uma RNA ¯aprende‖ através dessas conexões entre as camadas (preditores, oculta e resultados) e os pesos associados a cada camada. Sendo assim, um dado de entrada é apresentado na camada de preditores, sendo esse enviado camada a camada. O processamento matemático ocorre no envio de dados de uma camada a outra e os pesos dessas conexões são atualizados de acordo com o erro da camada de resultados, ou seja, a relação do resultado esperado e o resultado obtido. Esse processo é repetido até o valor do erro ser mínimo ou um valor especificado de interações[12,23,24].

Deep learning difere o seu aprendizado das técnicas mais tradicionais de ML, pois

processa modelos computacionais mais robustos e com múltiplas camadas de processamento baseadas em RNAs. Sendo assim, a técnica de deep learning funciona de acordo com uma RNA, mas possuindo um número maior de camadas ocultas e consequentemente de conexões sinápticas. Cada camada reproduz uma representação dos dados oriundos da camada anterior e seu algoritmo de aprendizado pode ser tanto supervisionado como não supervisionado[25,26].

Com o grande volume e a complexidade dos dados que envolvem trabalhar com big data, o algoritmo do *autoencoder* é um tipo de RNA que reduz a dimensionalidade dos dados, utilizando modelos matemáticos com alto grau de abstração para gerar um novo conjunto de dados reduzidos em dimensionalidade com representação o mais próxima possível dos dados de entrada. A diferença fundamental entre a RNA e o *autoencoder* é que o último utiliza em sua fase de treinamento dados não-rotulados[27].

O algoritmo da árvore de decisão é o mais utilizado quando o conjunto de dados é relativamente pequeno e pode ser utilizado com uma série de perguntas de sim/não para classificar os dados em categorias. Esse algoritmo utiliza um modelo estatístico para classificação ou predição de dados, utilizando a idéia de nós. Cada nó (pergunta) se divide em possíveis resultados e esses se ramificam em outras possibilidades, isso se repete até um desfecho final[16]. As principais vantagens deste algoritmo são sua simplicidade e interpretação intuitiva[28].

Random forests é uma ampliação do algoritmo da árvore de decisão, sendo bastante utilizado para resolução de problemas de classificação e regressão. As árvores de decisão são combinadas e cada árvore de decisão é treinada independentemente. Suas principais características são: teoria simples, velocidade rápida na análise dos dados, estabilidade com a presença de excesso de ruído e mecanismo de compensação automática em amostras tendenciosas dos dados[29].

A rede bayesiana é outra técnica muito aplicada à Medicina que consiste em métodos estatísticos bayesianos com uma fundamentação teórica que crenças subjetivas coerentes a especialistas de uma determinada área podem ser expressas em uma estrutura probabilística[17].

O SVM é um método de ML com aprendizado supervisionado, amplamente utilizado em bioinformática. Este algoritmo utiliza a ideia de minimização do erro e trabalha com teoria estatística do aprendizado e da otimização. Além da classificação binária, o SVM pode ser usado na regressão de dados contínuos, chamado de regressão do vetor de suporte (SVR). Os resultados obtidos com o uso do SVM são comparáveis aos de RNAs, apresentando processo de treinamento fácil e trabalhando com alta dimensionalidade de dados. Portanto, esse encontra um compromisso entre menor complexidade e erro[30,31].

Dessa forma, cada algoritmo utiliza técnicas distintas de como aprender com observações e como realizar um mapeamento do conjunto de preditores para o resultado final, a partir de rótulos criados em um modelo matemático. Este deve generalizar as informações, de modo que uma tarefa possa ser executada corretamente com entradas novas, não analisadas anteriormente pelo modelo[14].

3.2.3. *MACHINE LEARNING* NA MEDICINA

Desde o século passado, os pesquisadores exploram as diversas aplicações das técnicas de ML em todos os campos da Medicina[32]. A pesquisa médica envolvendo ML têm crescido exponencialmente ao longo das últimas décadas. Os dados do *PubMed(NCBI)* e *Medline,* envolvendo os descritores "*machine learning*", "*artificial intelligence*", "*unsupervised learning*", "*supervised learning*"e "*neural networks*", revelou 113.127 artigos publicados entre 1951 e 2019 (Gráfico 1). Ao acrescentar-se o descritor "*cardiology*" como condição obrigatória na pesquisa dos demais termos, 888 trabalhos retornam com distribuição semelhante à anterior, entre os anos de 1986 e 2019.

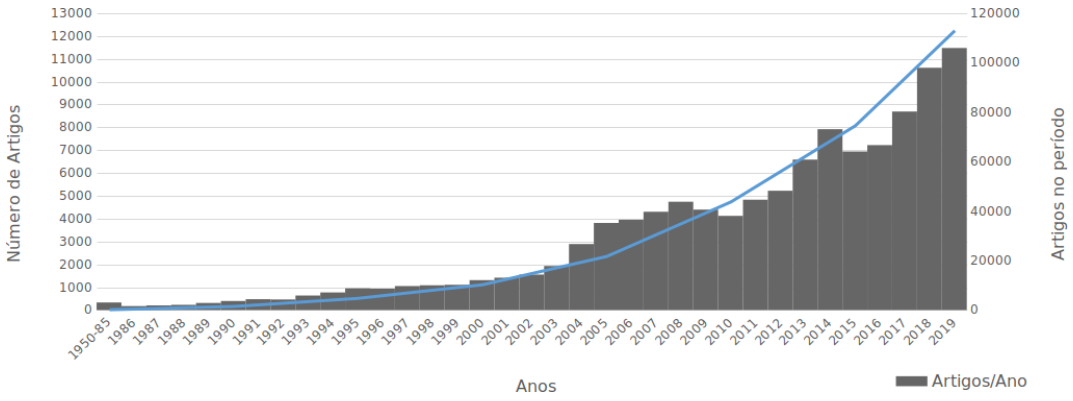

Gráfico 1. Número de artigos/ano e acumulado durante o período de 1951 a 2019 no *PubMed* e *Medline*

A capacidade dos algoritmos de ML de reconhecer padrões e predizer diagnóstico tem sido amplamente aplicada às diversas áreas de atenção à saúde[33-36]. Na Dermatologia, uma rede neural artificial foi capaz de diferenciar lesões dermatológicas em benignas versus malignas, a partir de mais de 129 mil casos, com resultados similares a um comitê de 21 dermatologistas[35]. No campo da Psiquiatria, o estudo com técnicas de ML reduziu o número de critérios diagnósticos de 29 para 8 com 100% de acurácia em 612 pacientes com diagnóstico firmado de transtorno do espectro autista[36].

A adição de tecnologias móveis - tais como: *smartphone* e *smartwatches* - aplicadas à área da saúde acrescentou mais uma dimensão ao ML, permitindo a leitura de grandes quantidades de dados pessoais em algoritmos de aprendizado[37]. Dentro de sistemas de *feedback*, a tecnologia móvel consegue ser um dispositivo biométrico (por exemplo, medir os níveis de glicose no sangue) com capacidade de direcionamento para intervenções clínicas em tempo real, baseadas em algoritmos que atualizam continuamente as informações pessoais do paciente[38]. A tecnologia pode simplificar os processos diagnósticos e facilitar a prática clínica.

3.2.4. *MACHINE LEARNING* NA CARDIOLOGIA

O avanço na capacidade computacional nas últimas décadas impactou especialmente o campo da detecção e predição de doenças cardiovasculares por meio da interpretação de dados complexos, como: estudos dos prontuários médicos, exames de imagem, banco de dados biológicos e genômicos e de avaliação molecular[32]. A cardiologia é uma das áreas de maior impacto na produção científica usando técnicas de ML (Tabela 2). Desde a predição de eventos cardiovasculares[39] à melhoria dos diagnósticos eletrocardiográficos e pelos métodos de imagem[40,41], a IA tem sido ferramenta importante para a pesquisa cientifica.

3.2.4.1. PROGNÓSTICO

Diversos escores de risco cardiovasculares foram desenvolvidos no intuito de predizer eventos cardiovasculares e identificarem os indivíduos com maior risco cardíaco para a prevenção primária[42]. No entanto, a despeito de todo o avanço propedêutico e terapêutico na Cardiologia, ainda há uma população em risco não identificada pelos métodos tradicionais[43]. O reconhecimento de potenciais fatores de risco não tradicionais é desejável e o uso de novas tecnologias, como a IA, torna-se método promissor nessa busca.

A predição de mortalidade por todas as causas no período de um ano, a partir da análise isolada do eletrocardiograma (ECG), apresentou resultados promissores (AUROC=0,87; $p<0,05$)[44]. É interessante ressaltar que uma análise cega destes ECG feita por três cardiologistas sugere que os padrões encontrados para predizer mortalidade pelo ML não são aparentemente visíveis pela avaliação médica convencional[44].

Em estudo com 2619 pacientes submetidos à tomografia computadorizada com emissão de prótons para a predição de risco cardiovascular, as técnicas de ML apresentaram melhores resultados (AUROC 0,81; $p<0.01$) do que a análise isolada do

exame[45].

Estudo com mais de 380.000 pacientes do Reino Unido avaliou o uso de técnicas de ML na predição do risco de eventos cardiovasculares em comparação com os algoritmos tradicionais propostos pelo *American College of Cardiology* e pela *American Heart Association*[39]. Houve melhoria de até 7,6% na predição de eventos com uso de RNA e algumas variáveis clínicas que não são valorizadas para doença cardiovascular pelos métodos tradicionais como depressão e uso de corticoides foram importantes para o risco cardiovascular avaliado pelas técnicas de ML[39]. Este achado foi corroborado por estudo multicêntrico americano em que os parâmetros encontrados para predição de risco cardiovascular diferem daqueles incluídos nas calculadoras de risco tradicionais[46].

A IA pode contribuir na geração de modelos preditivos mais complexos e específicos para cada indivíduo[47], com a incorporação dos componentes genômicos aos escores de risco cardiovascular[48,49]. A associação dos dados clínicos, sociais, demográficos e genéticos com os exames disponíveis pode permitir uma avaliação mais individualizada, visando à promoção de saúde[47].

3.2.4.2. DIAGNÓSTICO

As técnicas iniciais de ML foram aplicadas na análise e processamento de imagens[50]. Nos exames cardiológicos, a necessidade de uma equipe médica altamente especializada, variabilidade de laudos entre os médicos, além do tempo dispensado aos laudos motivaram o estudo das técnicas de ML como ferramenta diagnóstica[41,51].

Os estudos foram promissores e as modalidades da imagem cardíaca como ecocardiografia, tomografia computadorizada e ressonância nuclear magnética apresentaram boa acurácia em correlacionar alterações estruturais com a etiologia e fisiopatologia de doenças cardiovasculares[52,53]. Em um estudo com 159 pacientes, utilizaram-se três técnicas de ML para auxiliar na diferenciação ecocardiográfica entre

cardiomiopatia hipertrófica e hipertrofia fisiológica de atletas. Os parâmetros encontrados, como: a razão da velocidade transmitral diastólica precoce-tardia ($p < 0.01$), velocidade diastólica precoce (e') ($p < 0.01$) e a análise de *strain* ($p < 0.01$), foram melhores em sensibilidade e especificidade do que os tradicionalmente usados[52].

Um algoritmo de ML foi desenvolvido para diferenciar as estenoses coronarianas intermediárias pela angiografia com reserva de fluxo fracionada menor que 0,80 versus maior que 0,80, a partir de dados clínicos e angiográficos. Os resultados foram satisfatórios com acurácia de aproximadamente 80% para predição de reserva de fluxo fracionada menor que 0,8 (AUROC = 0,84-0,87, IC 95% 0,71-0,89). A validação externa do modelo desenvolvido também apresentou resultados similares em 79 pacientes de dois outros centros (AUROC = 0,89, IC 95% 0.83-0.95)[54].

Em relação à eletrocardiografia, estudos estão sendo desenvolvidos para melhoria dos diagnósticos automáticos[41]. Através de técnicas de ML, nosso grupo foi capaz de identificar seis classes eletrocardiográficas por meio da análise do ECG de 12 derivações com boa acurácia, comparável ao desempenho que residentes de Cardiologia do último ano[55]. Em pacientes com emergências cardiovasculares hospitalizados, ML teve uma acurácia diagnóstica de cerca de 90% para alterações maiores ao ECG[55]. Além disso, estudo recente foi capaz de identificar pacientes portadores de fibrilação atrial em ECGs em ritmo sinusal com uma sensibilidade de 79%, especificidade 79,5% e acurácia de 79,4%[56].

Tabela 2: Artigos com o uso das técnicas *Machine Learning* na Cardiologia

Artigo	Principais resultados
Can machine-learning improve cardiovascular risk prediction using routine clinical data? [38]	O algoritmo foi capaz de predizer 4998 de 7404 casos positivos (sensibilidade 67,5%, VPP 18,4%) e 53458 de 75585 casos negativos (especificidade 70,7% e VPN 95,7%), com ganho de 355 pacientes (+7,6%) que desenvolveram doenças cardiovasculares em relação ao método tradicional.

Deep neural networks can predict mortality from 12-lead electrocardiogram voltage data[43]	Por meio da análise isolada do ECG por algoritmo de ML, foi possível predizer mortalidade por todas as causas em um ano com AUC = 0,84 e p<0,05.
Phenomapping for the Identification of Hypertensive Patients with the Myocardial Substrate for Heart Failure with Preserved Ejection Fraction[57]	Um grupo de 1273 pacientes hipertensos foi avaliado por meio de técnicas de ML, utilizando dados clínicos, laboratoriais e ecocardiográficos. Foi possível identificar um grupo de pacientes com maior risco de desenvolver insuficiência cardíaca de fração preservada que, provavelmente, devem ser beneficiar de tratamento clínico mais intensivo.
Cognitive Machine-Learning Algorithm for Cardiac Imaging: A Pilot Study for Differentiating Constrictive Pericarditis From Restrictive Cardiomyopathy[58]	Utilizaram técnicas de ML para diferenciar pericardite constritiva de cardiomiopatia restritiva com uma curva ROC de 96,2% e acurácia superior a 90%.
Structured learning algorithm for detection of nonobstructive and obstructive coronary plaque lesions from computed tomography angiography[59]	O algoritmo de ML foi capaz de detectar lesões coronarianas superiores ou iguais a 25% com uma sensibilidade 93%, especificidade 95% e acurácia de 94% em 42 angiografias coronárias.
A deep neural network learning algorithm outperforms a conventional algorithm for emergency department electrocardiogram interpretation[55]	A análise automática pelo método de ML para a leitura de ECG em um departamento de emergência obteve sensibilidade (88,7% vs 92,0%, p < 0,086), especificidade (94% vs 84,7%, p < 0,0001), valor preditivo positivo (88,2% vs 75,4%, p < 0,0001) e acurácia (92,2% vs 87,2%, p < 0,0001) em relação ao método automático convencional.
Automatic Diagnosis of the Short-Duration 12-Lead ECG using a Deep Neural Network: the CODE Study[54]	Uma rede neural treinada foi capaz de detectar 6 classes de anormalidades eletrocardiográficas com especificidade superior a 99% e performance superior a 80%, comparada com residentes de cardiologia do último ano.
An artificial intelligence-enabled ECG algorithm for the identification of patients with atrial fibrillation during sinus rhythm: a retrospective analysis of outcome prediction[56]	Um software de ML foi capaz de detectar pacientes portadores de fibrilação atrial, a partir de ECG em ritmo sinusal com uma sensibilidade de 79%, especificidade 79,5% e acurácia de 79,4%.

3.2.5. LIMITES E DESAFIOS

A utilização das técnicas de ML é crescente, devido ao seu potencial para solucionar

problemas nas diversas áreas. Na Medicina, os resultados são promissores em diversas especialidades com a expectativa de que a IA possa ser ferramenta de auxílio para a prática clínica[3,60] . No entanto, ainda é necessária cautela na interpretação e incorporação dos resultados.

Os algoritmos de ML desenvolvidos devem ser reprodutíveis na população geral. Estudos com número pequeno de pacientes, em populações específicas ou com vieses de seleção não permitem a generalização dos seus achados[61,62]. Ainda que a captação de dados e sua interpretação tenham valor estatístico considerável, os melhores cenários ainda são incapazes de predizer o desfecho em pessoas diferentes[63].

O erro no processo automatizado pode induzir o profissional a conclusões incorretas, como demonstrado em estudo com 30 residentes em Clínica Médica que reduziram sua acurácia diagnóstica no laudo de ECG, após a disponibilização de laudos automáticos incorretos[64].

O avanço da IA na Medicina é visto com receio por alguns médicos. A posição alarmista de que ML possa substituir a figura do médico na atenção à saúde tem se mostrado injustificável. Nenhum *software*, até o momento, foi capaz de substituir o aspecto subjetivo da experiência clínica na tomada de decisões favoráveis ao paciente, exatamente, pela Medicina não ser uma ciência exata[55]. A negação ao avanço tecnológico e às ferramentas de IA hoje disponíveis têm potencial tão danoso quanto a sua total dependência no atendimento ao paciente. A combinação entre ML e o julgamento clínico tem apresentado melhores resultados em conjunto do que o seu uso isolado.[60]

3.2.6. CONCLUSÃO

O uso de técnicas de *Machine Learning* na Medicina deixou o campo teórico e se tornou uma realidade. Estudos mostram a sua aplicabilidade clínica com impacto na

avaliação diagnóstica e prognóstica. O processo da integração da ML na Medicina ainda está em desenvolvimento. A sua utilização com todos os potenciais benefícios dependerá da capacidade e da criatividade humana no processo de otimização da sua técnica. Conhecer o conceito de ML, seu panorama e perspectivas é essencial para o profissional que deseja praticar uma Medicina atualizada e individualizada.

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4. OBJETIVOS

4.1. OBJETIVO GERAL

- Avaliar marcadores eletrocardiográficos como preditores independentes de mortalidade na população do estudo CODE.

4.2. OBJETIVOS ESPECÍFICOS

- Avaliar a presença de alterações eletrocardiográficas maiores como fatores de risco independentes para mortalidade geral e cardiovascular, ajustadas por idade, sexo e comorbidades, nos pacientes da RTMG de 2010 a 2017;

- Avaliar a idade eletrocardiográfica predita por ML como fator de risco independente para mortalidade geral nos pacientes dos estudos CODE, Estudo Longitudinal de Saúde do Adulto (ELSA-Brasil) e São Paulo-Minas Gerais *Tropical Medicine Research Center* (SaMiTrop);

- Descrever a acurácia da idade predita pelo ECG por ML nos pacientes dos estudos CODE, ELSA-Brasil e SaMiTrop.

5. METODOLOGIA

5.1. DESENHO DO ESTUDO:

Trata-se de coorte retrospectiva de pacientes atendidos na atenção primária de municípios de Minas Gerais, cujos ECGs foram analisados por cardiologistas da RTMG entre 2010 e 2017. A RTMG, atualmente, abrange 817 dos 853 municípios de Minas Gerais e já realizou mais de cinco milhões de ECG desde a sua implementação.

5.2. CRITÉRIOS DE INCLUSÃO

Foram incluídos no estudo pacientes maiores de 16 anos com ECG de 12 derivações realizado na RTMG entre 2010 e 2017. Para a análise específica de pré-excitação ventricular, todas as faixas etárias foram incluídas.

5.3. CRITÉRIOS DE EXCLUSÃO

Exames sem registro de batimentos cardíacos (isoelétricos), com interferências, troca ou mau posicionamento de eletrodos, que comprometeram a análise, foram excluídos. Para a análise das alterações eletrocardiográficas, os pacientes que realizaram mais de um ECG, somente o primeiro exame foi analisado e os subsequentes foram excluídos.

5.4. COLETA DE DADOS

Todos os municípios assistidos pelo programa receberam aparelho de eletrocardiograma digital de doze derivações das marcas Micromed (Brasília) ou TEB (São Paulo) com software específico de captura dos eletrocardiogramas, desenvolvido

pela própria RTMG. Esse software permite a obtenção do traçado do ECG e de dados clínicos, sendo enviados por meio da internet para um servidor central no Centro de Telessaúde do Hospital das Clínicas da Universidade Federal de Minas Gerais. Com o uso do software específico de leitura dos ECGs, associado a ferramentas de mensuração e magnificação, os exames foram analisados por uma equipe de cardiologistas experientes em eletrocardiografia da RTMG, conforme rotina assistencial e com a geração de um laudo textual.

A anamnese e todos os dados dos pacientes foram coletados pelo profissional de saúde solicitante. Todos os exames realizados no período foram guardados em banco de dados específico. As seguintes variáveis foram incluídas:

- Dados do paciente: nome, data nascimento, idade, sexo, comorbidades (hipertensão arterial sistêmica, doença de Chagas, diabetes mellitus, dislipidemia, doença pulmonar obstrutiva crônica, infarto do miocárdio prévio e tabagismo);

- Dados do exame: data de realização, município e laudo do cardiologista no formato texto-livre não estruturado.

O programa *Glasgow University Interpreter* foi rodado em toda a amostra e utilizado para análise morfológica dos traçados eletrocardiográficos por meio de padrões rígidos de interpretação. O software avalia o valor de todos os intervalos (PR, RR, QT, QT corrigido pelo método de Framingham), eixo e duração do complexo QRS e das ondas P e T, frequência cardíaca sinusal e ventricular. O programa também exporta interpretação sucinta com as principais alterações eletrocardiográficas identificadas codificadas pelos sistemas Glasgow e Minnesota.

5.5. DESCRIÇÃO DA ANÁLISE DE DADOS

5.5.1. DEFINIÇÃO DOS CASOS DE ALTERAÇÕES ELETROCARDIOGRÁFICAS MAIORES

As alterações maiores eletrocardiográficas consideradas na tese foram: bloqueio de ramo direito, bloqueio de ramo esquerdo, bloqueios atrioventriculares de 1º, 2º e 3ºgrau e pré-excitação ventricular.

Para a obtenção do diagnóstico eletrocardiográfico das anormalidades, a partir do laudo eletrocardiográfico em texto, os laudos foram processados por um software automático de classificação baseado em aprendizado de máquina, chamado *Lazy Associative Classifier* (LAC)(69)(70)(71). A conclusão do laudo médico é, inicialmente, tratada com a retirada das palavras de paradas, como: a, as, os, de, com, sem e para. Posteriormente, geram-se n-gramas que é uma forma de agrupar palavras para o processamento no LAC. Os resultados foram submetidos a algoritmos de decisões para a obtenção final das classes diagnósticas. Esses algoritmos são treinados, usando a base de dados original. Em amostra de 4.557 ECG do nosso banco de dados, que foram manualmente classificados, observou-se acurácia de 99%, valor preditivo positivo de 100% e sensibilidade e especificidade de 99% para o diagnóstico das anormalidades eletrocardiográficas incluídas(72).

O diagnóstico das anormalidades eletrocardiográficas foi aceito, sem revisão manual, quando havia concordância no laudo do cardiologista com um dos sistemas automáticos (*Minnesota ou Glasgow*). Os exames com laudo por somente um dos sistemas automáticos foram desconsiderados como portadores da anormalidade eletrocardiográfica. Na zona cinzenta, ficaram os ECG em que somente o cardiologista laudou ou dois sistemas automáticos consideraram. Estes foram revisados manualmente por uma equipe treinada. Para BRE e BRD, 17.903 exames foram revisados enquanto para BAV 9.038 e para pré-excitação ventricular 1090 traçados.

5.5.2. DESCRIÇÃO DA TÉCNICA DE *MACHINE LEARNING*

A técnica de ML utilizada foi a rede neural convolucional, com uma arquitetura conhecida como rede neural residual(73). Todos os traçados eletrocardiográficos foram extraídos em uma frequência de 400 Hz, com duração de 7 a 10 segundos, o que resultou em um sinal com 4096 amostras para cada derivação. Esse sinal foi importado para a rede neural.

A arquitetura e a definição dos hiperparâmetros para a rede são similares à metodologia de estudo prévio(74), em que a rede neural convolucional foi treinada no mesmo banco de dados de ECG para detecção de seis anormalidades eletrocardiográficas (Figura 3).

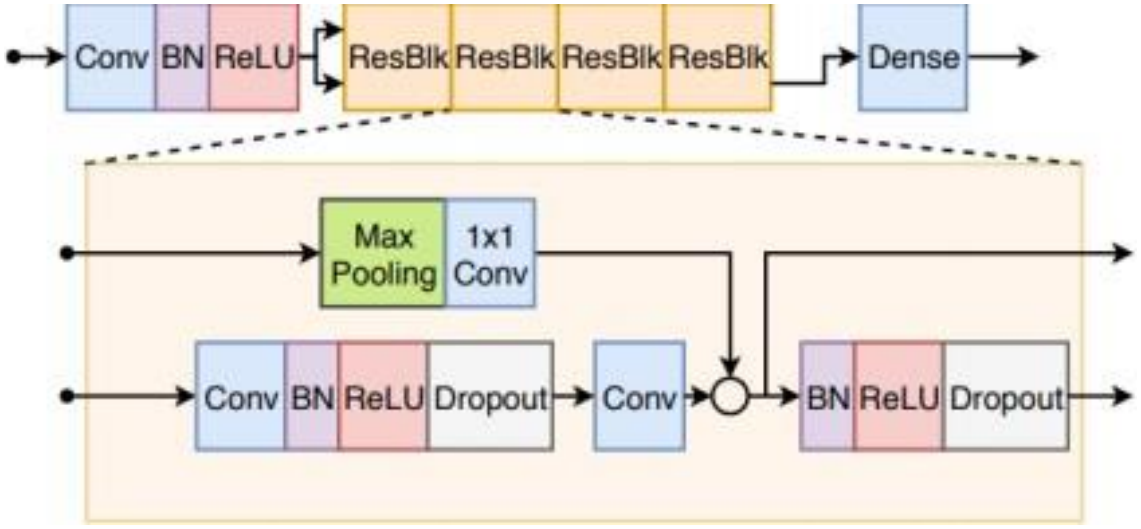

Figura 3. Arquitetura da rede neural residual

A base de dados de ECG foi dividida em três, sendo 80% para treinamento, 5% para validação e 15% para teste. Dessa forma, 80% dos dados foram usados para aprender os pesos da rede neural, 5% para comparar os resultados iniciais e 15% para avaliar a performance final do modelo. A distribuição da idade da população estudada é heterogênea. No intuito de uniformizar, 6830 exames de pacientes com idade entre 16 a 85 anos foram escolhidos, aleatoriamente, para compor a base de validação e de teste.

Os 80% restantes foram alocados para o treino da rede neural. Como a base de treino ficou heterogênea em relação à idade dos pacientes, estabeleceram-se pesos diferentes para cada ECG, inversamente proporcionais à frequência da idade na base.

O modelo foi validado em duas coortes externas: uma composta por servidores públicos de universidades federais brasileiras (ELSA-Brasil(75)) e a outra por pacientes portadores de cardiomiopatia chagásica (SaMi-Trop(76)). Os traçados eletrocardiográficos dos pacientes realizados na visita inicial, bem como dados clínicos e o desfecho desfecho de mortalidade foram disponibilizados para a análise.

5.5.3. DESFECHOS

O desfecho primário do estudo foi mortalidade geral. Apenas para as alterações eletrocardiográficas: bloqueio de ramo esquerdo e direito, considerou-se um desfecho secundário que foi a mortalidade cardiovascular. Consideraram-se todos os códigos da CID como causa básica da declaração de óbito para mortalidade geral. Para mortalidade cardiovascular, foram consideradas as nove causas globais mais comuns de morte relacionadas com doença cardiovascular(4). A causa básica da declaração de óbito foi definida como cardiovascular pela categorização dos códigos da CID. Essas causas foram: doença cardíaca reumática (códigos I01-I01.9, I02.0, I05-I09.9), cardiopatia isquêmica (códigos CID10 I20-I25.9), doença cerebrovascular (G45-G46.8, I60-I61.9, I62.0, I63-I63.9, I65-I66.9, I67.0-I67.3, I67.5-I67.6, I68.1-I68.2, I69.0-I69.3),doença cardíaca hipertensiva (I11), cardiomiopatia e miocardite (A39.52, B33.2-B33.24, D86.85, I40-I43.9, I50, I51.4-I51.5), fibrilação atrial e flutter (I48), aneurisma de aorta (I71), doença vascular periférica (I70.2-I70.7, I73-I73.9) e endocardite (A39.51, I33- I33.9,I38-I39.9).

5.5.4. PAREAMENTO DAS BASES DE DADOS

O método de pareamento probabilístico se baseia na probabilidade de concordância ou não entre variáveis comuns de diferentes bancos de dados, de forma que é possível determinar qual a probabilidade de um par de registros corresponder a um mesmo indivíduo.

O banco de dados do ECG foi associado por meio de relacionamento probabilístico de registros pelo programa FRIL (*Fine-grained record linkage software*, v.2.1.5, Atlanta, GA) com os dados do SIM do estado de Minas Gerais, os quais foram obtidos, a partir de informações contidas na Declaração de Óbito. As variáveis utilizadas foram nome e último sobrenome, data de nascimento, sexo e município de residência do paciente.

A primeira etapa do relacionamento consistiu na padronização dos campos e foi feita automaticamente pelo programa, a fim de minimizar a ocorrência de erros. Nomes dos pacientes e dos municípios tiveram os seus caracteres transformados em maiúsculos, eliminados os conectivos, pontuação, espaços em branco no início dos campos, preposições, acentos, cedilhas, algarismos e símbolos (¯DE, DA, DO, DOS, DAS, @, #, $, %,[ ],*,(),=,+,1,2,3,4,5,6,7,8,9,0,\ ?/' :;.-!"_‖).

O algoritmo de codificação fonética Soundex é um discriminador de nomes que foi aplicado para corrigir pequenas diferenças na grafia e pronúncia dos mesmos e, sumariamente, os transforma em códigos constituídos de até quatro dígitos, por exemplo, João e Daniella seriam codificados em ¯J00‖ e ¯D54‖, respectivamente. Sexo foi codificado em ¯F‖ para feminino e ¯M‖ para masculino, e a data de nascimento foi padronizada em DD-MM-AAAA.

Posteriormente, foi realizada blocagem para evitar que sejam realizadas comparações de registros que possuem alta probabilidade de não serem pares verdadeiros, agilizando o procedimento. Assim, por exemplo, dividir em blocos de acordo

com o último nome evitaria comparar indivíduos cujos sobrenomes são diferentes e, portanto, possuem baixa probabilidade de serem a mesma pessoa.

A última etapa consistiu em parear e identificar os pares de registros concordantes. O programa constrói um escore final para cada par, com finalidade de estimar a probabilidade de ser a mesma pessoa. O ponto de corte definido foi de 94 e valores acima e abaixo delimitam as faixas de pares verdadeiros e falsos, respectivamente.

5.6. ANÁLISE ESTATÍSTICA

Variáveis qualitativas foram descritas pela distribuição de frequência. Dados obtidos de variáveis quantitativas contínuas foram expressos como média e desvio padrão ou mediana com intervalo interquartil.

Para o estudo das anormalidades eletrocardiográficas, o tempo decorrido entre a data de realização do eletrocardiograma (evento índice) e o evento de interesse (data do óbito) foi considerado variável dependente. A presença da anormalidade eletrocardiográfica foi variável independente, juntamente com as características clínicas da população. O grupo de comparação: pacientes sem as alterações maiores eletrocardiográficas que incluiu tanto aqueles com ECG normal, quanto, com outras anormalidades. Pacientes que não apresentaram o evento de interesse até o final do seguimento foram censurados, mas contribuíram com tempo de acompanhamento até a data final do estudo (setembro de 2017).

Em relação à análise da idade do ECG por ML, o coeficiente de determinação e o erro médio entre a estimativa da idade eletrocardiográfica e a idade real foram utilizados para avaliar a rede. A seguir, a variável ECG-idade calculada por ML foi considerada a variável independente, considerando-se o desfecho o tempo entre o ECG e o evento morte por todas as causas.

O método não paramétrico de *Kaplan-Meier* foi utilizado para calcular sobrevida. O nível de significância estatística foi definido para valores de p menores que 0,05, calculados pelo teste *Logrank*. O modelo multivariado de regressão proporcional de *Cox* e o modelo de *Log-normal* foram usados. As análises foram ajustadas pela idade, sexo e comorbidades. O programa estatístico R (versão 3.4.3, Viena, Áustria) foi utilizado para todas as análises.

5.7. ASPECTOS ÉTICOS

Considerando-se os termos da Resolução no 466/12 do Conselho Nacional de Saúde, todos os aspectos éticos desta legislação foram preservados ao envolver seres humanos como sujeitos de pesquisa. O projeto foi aprovado no Comitê de Ética em Pesquisa da Universidade Federal de Minas Gerais (CAAE: 68496317.7.0000.5149)(77). Os resultados do estudo foram divulgados assegurando-se que nenhuma forma de identificação individual fosse exposta.

6. RESULTADOS E DISCUSSÃO

Os resultados e a discussão serão apresentados em formato de artigos científicos.

6.1. ARTIGO 1

Publicado na *Journal of Electrocardiography* (aceito 04 de setembro de 2019)

Evaluation of mortality in bundle branch block patients from an electronic cohort: Clinical Outcomes in Digital Electrocardiography (CODE) study

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*The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Abstract

Background: Left bundle branch block is recognized as a marker of higher risk of death, but the prognostic value of the right bundle branch block in the general population is still controversial. Our aim is to evaluate the risk of overall and cardiovascular mortality in patients with right (RBBB) and left bundle branch block (LBBB) in a large electronic cohort of Brazilian patients.

Methods: This observational retrospective study was developed with the database of digital ECGs from Telehealth Network of Minas Gerais, Brazil (TNMG). All ECGs performed from 2010 to 2017 in primary care patients over 16 years old were assessed. The electronic cohort was obtained by linking data from ECG exams (name, sex, date of birth, city of residence) and those from national mortality information system, using standard probabilistic linkage methods (FRIL: Fine-grained record linkage software, v.2.1.5, Atlanta, GA). Only the first ECG of each patient was considered. Clinical data were self-reported, and ECGs were interpreted manually by cardiologists and automatically by the Glasgow University Interpreter software. Hazard ratio (HR) for mortality was estimated using Cox regression.

Results: From a dataset of 1,773,689 patients, 1,558,421 primary care patients over 16 years old underwent a valid ECG recording during 2010 to 2017. We excluded 17,359 patients that didn´t have a valid QRS measure from the Glasgow program and 11,091 patients from the control group that had QRS equal or above 120 ms and were not RBBB or LBBB. Therefore, 1,529,971 were included (median age 52 [Q1:38; Q3:65] years; 40.2% were male). In a mean follow-up of 3.7 years, the overall mortality rate was 3.34%. RBBB was more frequent (2.42%) than LBBB (1.32%). In multivariate analysis, adjusting for sex, age and comorbidities, both patients with RBBB (HR 1.32; CI95% 1.27-1.36) and

LBBB (HR 1.69; CI95% 1.62-1.76) had higher risk of overall mortality. Women with RBBB had an increased risk of all-cause death compared to men (p<0.001). Cardiovascular mortality was higher in patients with LBBB (HR 1.76; CI 95% 1.55-2.01), but not for RBBB.

Conclusions: Patients with RBBB and LBBB had higher risk of overall mortality. Women with RBBB had more risk of all-cause death than men. LBBB was associated with higher risk of cardiovascular mortality.

Key words: electronic cohort, electrocardiogram, sex, bundle branch block, mortality, cardiovascular mortality, Chagas disease

Introduction:

Bundle branch block has been associated with worse prognosis in cardiac disease, especially in heart failure[1]. Left bundle branch block (LBBB) is a known predictor of cardiac events in coronary heart disease[2], heart failure[3] and also in general population[4][5]. However, there are controversial data regarding right bundle branch block (RBBB), considered to be benign in asymptomatic healthy individuals[6]. Although, one study conducted in the general population showed that RBBB was associated with higher risk in all-cause and cardiovascular mortality[7]. For coronary heart disease and heart failure, the prognostic meaning of RBBB also has conflicted findings in the literature[5][8].

Most previous findings came from epidemiological studies or case series. More recently, large databases of digital electrocardiograms (ECG) were linked to mortality databases, what was called an electronic cohort. Big data provided from electronic cohorts with a large amount of information have more reliable and applicable results to the general population[9]. Our aim was to evaluate the overall and cardiovascular mortality in bundle branch block patients from a large electronic cohort composed by primary care patients.

Methods:

We conducted an observational retrospective study using database of digital ECGs from the Telehealth Network of Minas Gerais (TNMG)[10]. This public Brazilian telehealth system has performed more than 4 million ECGs since its inception, in 2006, and is responsible for the ECG report of more than 900 municipalities in Brazil.

All ECGs performed by the TNMG from patients of at least 16 years-old from 2010 to 2017 were assessed. The majority of patients (79%) underwent routine ECG. Exams without valid tracings or with technical problems were excluded. In patients who underwent more than one ECG, only the first exam was analyzed. ECGs were performed by the local primary care professional, using digital electrocardiographs by *Tecnologia Eletrônica Brasileira* model ECGPC (São Paulo, Brazil) or *Micromed Biotecnologia* model *ErgoPC 13* (Brasilia, Brazil).

Clinical data (age, sex and comorbidities) were collected using a standardized questionnaire. Clinical conditions included self-reported smoking, hypertension, diabetes, dyslipidemia, Chagas disease, previous myocardial infarction and chronic obstructive pulmonary disease.

A specific software, developed in-house, was capable to capture ECG tracing, upload the ECG and the patient‘s clinical history and, then, send to the TNMG analysis center thought the internet. The clinical information, ECGs tracings and reports were stored in a specific database. For the purpose of the present study, the Glasgow 12-lead ECG analysis program (release 28.4.1, issued on June 16th 2009) was used to automatically interpret all ECGs available in the database, exporting the diagnosis, codified by both Glasgow and Minnesota codes[11].

ECGs were analyzed by a team of fourteen trained cardiologists using standardized criteria[12]. Each ECG was interpreted by only one cardiologist. RBBB was

considered if QRS duration was greater than or equal to 120 ms, presence of rsr, rsR, or rSR morphologies in leads V1 or V2 and S wave of greater duration than R wave or greater than 40 ms in leads I and V6. LBBB was considered if QRS duration greater than or equal to 120 ms, presence of broad notched or slurred R wave in leads I, aVL, V5, and V6, absence of q waves in leads I, V5, and V6 and R peak time greater than 60 ms in leads V5 and V6.

The ECG medical report was done as an unorganized free text. In order to recognize RBBB and LBBB diagnosis among these million reports, a hierarchical free-text machine learning was used. First, the text was preprocessed by removing stop-words and generating n-grams. Then, we used the classification model called Lazy Associative Classifier [13–15], which was built with a 2800-sample dictionary manually created by specialists based on text from real diagnoses. The final report was obtained by imputing the Lazy Associative Classifier results to a decision tree for class disambiguation. The decision tree was trained using the original dataset. The classification model was tested on 4557 medical reports manually labeled by two cardiologists with 99% accuracy, 100% positive predictive value and 99% sensibility.

Electrocardiographic diagnosis of RBBB and LBBB were considered automatically when there was agreement between cardiologist report and automatic report from Glasgow or Minnesota code. In the 17,903 cases where there were discordances between medical report and one of the automatic programs, a manual revision was done by trained staff. Those where RBBB and LBBB were diagnosed only by one of the automatic systems were not considered (Figure 1). The ECGs that were not classified as RBBB or LBBB and had QRS duration lower than 120 ms were included in the control group.

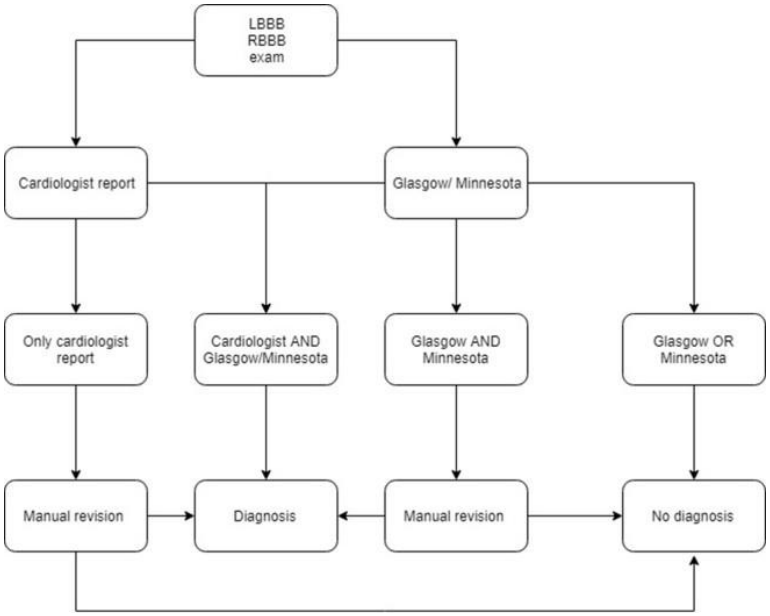

Figure 1- Diagram for bundle branch block diagnosis in the ECG database

The electronic cohort was obtained linking data from the ECG exams (name, sex, date of birth, city of residence) and those from the national mortality information system, using standard probabilistic linkage methods (FRIL: Fine- grained record linkage software, v.2.1.5, Atlanta, GA).

The primary end point was all-cause mortality. Secondary end point was cardiovascular mortality, defined by nine groups of cardiovascular disease through the International Classification of Diseases (ICD) coding: rheumatic heart disease (I01-I01.9, I02.0, I05-I09.9), ischemic heart disease (I20-I25.9), cerebrovascular disease (G45-G46.8, I60-I61.9, I62.0, I63-I63.9, I65-I66.9, I67.0-I67.3, I67.5-I67.6, I68.1-I68.2, I69.0-I69.3), hypertensive heart disease (I11), myocarditis (A39.52, B33.2-B33.24, D86.85, I40-I43.9, I51.4-I51.5), atrial fibrillation or flutter (I48), aortic aneurysm (I71), peripheral artery disease (I70.2-I70.7, I73-I73.9) and endocarditis (A39.51, I33-I33.9,I38-I39.9)[16].

R program (version 3.4.3, Vienna, Austria) was used for statistical analysis. Categorical data were reported as counts and percentages; continuous variables were reported as mean and SD or median (25th, 75th percentiles), as appropriated. To assess

the relation between RBBB, LBBB and mortality, Cox regression was used, adjusted by age, sex and clinical conditions (smoking, hypertension, diabetes, dyslipidemia, Chagas disease previous myocardial infarction and chronic obstructive pulmonary disease and). Confidence interval of 95% was used. Two-tailed P-value of 0.05 was considered statistically significant. In addition, to examine the association between ECG and all-cause mortality, survival curves were computed using Kaplan-Meier estimates.

This study was approved by the Research Ethics Committee of the Federal University of Minas Gerais.

Results:

From a dataset of 1,773,689 patients, 1,558,421(87.8%) primary care patients over 16 years old underwent a valid ECG recording during 2010 to 2017. We excluded 17,359(1.0%) patients that didn´t have a valid QRS measure from the Glasgow program and 11,091(0.6%) patients from the control group that had QRS equal or above 120 ms and were not RBBB or LBBB. Therefore, 1,529,971(86.2%) were included (median age 52 [Q1:38; Q3:65] years; 40.2% were male). The prevalence of RBBB (2.42 %) was higher than LBBB (1.32%). The overall mortality rate was 3.31% in a mean follow-up of 3.7 years.

RBBB patients had a median age of 65 [Q1:54; Q3:75] years with 48.3% female. All comorbidities were associated with RBBB. Chagas disease showed the strongest association (Table 1). LBBB patients were older (median age 70 [Q1:60; Q3:78] years) and mostly women (61.7%). All clinical conditions were associated with LBBB. Myocardial infarction and Chagas disease had the strongest association (Table 1).

Table 1- Baseline data by prevalence of bundle branch block

Variable	**Control group (n=1,472,678)**	**LBBB (n=20,226)**	**RBBB (n=37,031)**	**Adjusted* OR LBBB**	**Adjusted* OR RBBB**	**p-value**
Age (years)	51(38-64)	70(60-78)	65(54-75)	-	-	**<0.001**
Male sex	588,393 (40.0%)	7,752 (38.3%)	19,178 (51.7%)	-	-	**<0.001**
Current smoking	103,181 (7.01%)	1,178 (5.82%)	3,000 (8.09%)	**0.90 (0.85-0.96)**	1.11 (1.07-1.15)	<0.001
Hypertension	458,531	9,826	17,184	1.26	1.34	**<0.001**

	(31.1%)	(48.6%)	(46.4%)	(1.22-1.29)	(1.32-1.37)	
Diabetes	94,734 (6.43%)	2,131 (10.5%)	3,188 (8.60%)	1.20 (1.14-1.25)	1.08 (1.04-1.12)	**<0.001**
Dyslipidemia	56,479 (3.84%)	1,276 (6.31%)	2,005 (5.41%)	1.22 (1.15-1.29)	1.15 (1.10-1.21)	**<0.001**
Chagas disease	26,149 (1.78%)	938 (4.64%)	6,768 (18.3%)	**2.21 (2.06-2.36)**	**11.60 (11.26-11.95)**	**<0.001**
Myocardial infarction	10,443 (0.71%)	422 (2.09%)	493 (1.33%)	**2.21 (1.99-2.43)**	1.41 (1.29-1.54)	**<0.001**
COPD	10,388 (0.71%)	257 (1.27%)	416 (1.12%)	1.23 (1.08-1.39)	1.20 (1.08-1.32)	**<0.001**

Data are present as median (Q1-Q3) or number (%)

OR,odds ratio; CI confidence interval; COPD, chronic obstructive pulmonary disease;

*Adjusted for sex and age

In a multivariate analysis, adjusted by sex, age and clinical conditions, RBBB and LBBB showed an increased risk of all-cause mortality. LBBB (HR 1.69, 95% CI 1.62-1.76; p-value <0.001) had a higher risk than RBBB (HR 1.32, 95% CI 1.27-1.36; p-value <0.001) (Table 2; Figure 2).

Only sex had an interaction in overall mortality analyses in patients with RBBB (p-value=0.0004). Therefore, women had an increased risk of all-cause deaths (HR 1.39, 95% CI 1.31-1.47) than men (HR 1.29, 95% CI 1.23-1.35; p-value <0.001).

For cardiovascular mortality, LBBB was an independent risk factor (HR 1.76, 95% CI 1.55-2.01; p-value <0.001), and RBBB did not achieve statistical significance (HR 1.12, 95% CI 0.99-1.28; p-value 0.06) (Table 2; Figure 2).

Table 2- Prognostic value of bundle branch block for mortality

Type of event	LBBB (HR CI 95%)	p-value	RBBB (HR CI 95%)	p-value
Death for all causes+	1.69 (1.62-1.76)	<0.001	1.32 (1.27-1.36)	<0.001
Cardiovascular death +	1.76 (1.55-2.01)	<0.001	1.12 (0.99-1.28)	0.06

HR, hazard ratio; CI, confidence interval

+ adjusted for age, sex and comorbidities

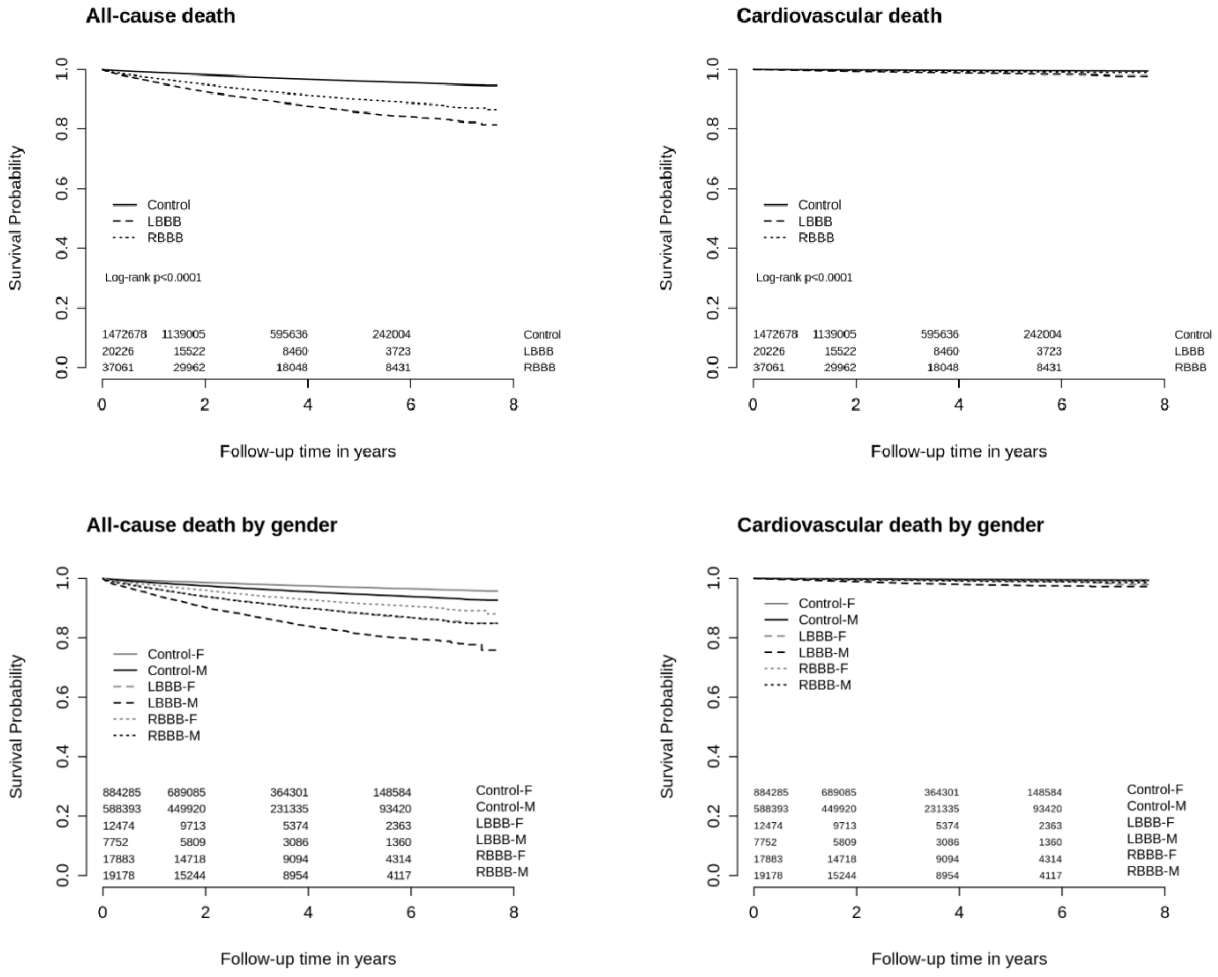

Figure 2- Kaplan-Meier curves for overall and cardiovascular mortality in LBBB and RBBB, according to sex

Discussion:

Our study showed that the presence of bundle branch block has prognostic significance in a very large population derived from primary care setting. Both RBBB and LBBB were independent risk factors for all-cause mortality. Female sex had increased risk of all-cause deaths in patients with RBBB. LBBB, but not RBBB, was associated with increased risk of cardiovascular mortality.

The prevalence of RBBB and LBBB was significantly higher in this sample than in others studies conducted in the general population[5][7][17]. One possible reason is the high prevalence, in the territory covered by the TNMG, of Chagas disease, a chronic infectious disease, known to cause intraventricular disturbances, specially RBBB[18]. It is endemic disease in Latin America countries, but it is becoming a worldwide health problem due to the increasing flow of migration to developed countries [19]. Furthermore, in our cohort, we included patients with known cardiovascular diseases, differently from the other studies[7][17]. We found that RBBB was associated with increased risk in overall mortality. In the Copenhagen City Heart Study[7], conducted in 18,441 patients, there was also an increased risk for overall mortality in RBBB, differently from the findings of Fleg *et al* in healthy men [6]. There is no available evidence that explains the difference between sex in the RBBB patients. Further studies should be done to confirm this finding.

Regarding cardiovascular mortality, we found no association with RBBB, opposite to the Copenhagen study [7]. This controversial data can be due to the different definition of cardiovascular mortality adopted. They used all codes in the group of diseases of the circulatory system (ICD-8: 390–459; ICD-10: I00–99) and we used the classification of Global Burden of Diseases[16] for cardiovascular mortality. Furthermore, they only adjusted for age, body mass index and systolic blood pressure in the Cox regression for

cardiovascular mortality. Similarly to our study, RBBB did not have an impact on cardiovascular mortality either in patients with or without previous heart disease in the Finnish population[5].

LBBB is a well-known marker of cardiac disease with evidence of worse cardiac prognosis[4]. Many of these prognostic evidences come from selected patients with heart failure[20] or myocardial infarction[2] in hospitalized patients. We studied a very large sample of patients attended at primary health care centers and we also found increased risk of mortality in those with LBBB. Similarly, a study conducted in Finnish general population found a significant hazard ratio of 2.11 for cardiovascular mortality and an increased risk for overall mortality[5].

Our study has limitations. Comorbidities data were self-reported and thus might have been underreported. The clinical data came from a predetermined questionnaire not tailored for the study, therefore, some important variables with impact on the prognosis of bundle branch block, such as heart failure, were unavailable and not considered as comorbidities in the multivariate analysis. The software Lazy Associated Classificator used for ECG report classification has good accuracy, sensibility and positive predictive value, but can have errors. In order to minimize this problem, we included the automatic classification of Glasgow and Minnesota to the diagnostic algorithm. Furthermore, manual revision was done in more than 15,000 ECG to confirm the presence of bundle branch block. The quality of the data from the national mortality information system varies according to the region of the state of Minas Gerais and, therefore, misclassification in basic cause of death can occur. The probabilistic linkage also has some issues as a less than perfect sensitivity and the possibility of false pairs. Therefore, we defined a high cut off point for true pairs and made a manually revision for the doubtful cases.

Despite the limitations, our study was innovative because was the first to assess

mortality in bundle branch block in a large Latin America sample from primary care centers. Further, we had a reasonable number of Chagasic patients that have not been evaluated in the previous studies. As the study involves a large electronic cohort with millions of patients, we believe that our findings are consistent and bring new evidence in the literature.

Conclusions

LBBB and RBBB increased the risk of all-cause mortality in patients of Brazilian primary care centers. Women with RBBB had higher risk of all-causes deaths than men. LBBB, and not RBBB, was associated with increased risk of cardiovascular mortality.

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6.2. ARTIGO 2

Association between atrioventricular block and mortality in primary care patients: the CODE study

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*The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Abstract

Introduction: Atrioventricular (AV) heart block describes an impairment of conduction from the atria to the ventricles via the AV junction. Its prevalence varies according to the degree of the block and the population studied. Although the clinical course of AV block has been evaluated in some studies, the findings are from high-income countries and, therefore, cannot be extrapolated to the Latin population.

Objective: Evaluate the association between AV block and overall mortality of patients from Telehealth Network of Minas Gerais (TNMG), Brazil.

Methods: This is an observational study with patients from the CODE cohort study, older than 16 years who underwent digital electrocardiogram (ECG) by TNMG from 2010 to 2017. Clinical data were self-reported. ECGs were reported by trained cardiologists and also interpreted by Glasgow and Minnesota automated software. Only the first ECG of each patient was analyzed. To assess the relationship between AV block and mortality, the Log-normal model and the Kaplan Meier curves were used.

Results: A total of 1,557,901 patients were included; 40.2% men with a mean age of 51. 7 (SD+ -17.6) years. In a mean follow-up of 3.7 years, the mortality rate was 3.35%. The AV block prevalence was 1.38% (21,538); 1.32% (20,644) corresponding to first-degree AV block, 0.02% (273) to second and 0.04% (621) to third-degree AV block. After adjustment for sex, age and clinical conditions, patients with first-degree, second and third- degree AV block were associated with 24% (RS = 0.76; 95% CI: 0.71-0.81; p<0.001), 55% (RS = 0.45; 95% CI: 0.27-0.77; p=0.01) and 64% (RS = 0.36; 95% CI: 0.26-0.49; p<0.001) lower survival rate when compared to control, respectively. Patients with 2:1 AV block had 79 % (RS = 0.21; 95% CI: 0.08-0.52; p=0.005) lower survival rate than the control group. Only

the second-degree Mobitz type I was not associated with higher mortality (p = 0.27). **Conclusion:** AV block was an independent risk factor for overall mortality, with the exception for second-degree Mobitz type I.

Keywords: Atrioventricular block, Electrocardiography, Mortality.

Introduction

The atrioventricular (AV) node is responsible for the electrical connection between the atria and ventricles. (1). The presence of delay or interruption in the AV conduction is called AV block (AVB)(2) that is classified into three degrees, according to the ECG presentation(3). The known causes of AVB are several and include ischemic heart disease, degenerative conduction system disease, congenital heart disease, connective tissue disease, inflammatory diseases, medications and increased autonomic tonus(4).

AVB prevalence varies between 0.6% to 6.04% in the literature, depending on the population studied and the AVB degree(5)(6). The prevalence is usually higher in elderly and in men(5). First-degree AVB is the most common and can be frequently found in outcome patients(4).

The clinical course of first-degree AVB has been evaluated in studies from community based samples, as the Framingham cohort(4). Patients with first-degree AVB have a higher risk of atrial fibrillation(7), death, stroke or hospitalization for heart failure(8). It is also described that in acute myocardial infarction patients, high-degree AVB is associated with an increased risk of morbidity and mortality(9).

Nonetheless, there is no prospective study in the prognostic value of all degrees of AVB in a general population, what limit the understanding of the significance of these abnormalities in an outpatient setting. Indeed, previous studies from our group showed that ECG abnormalities that are considered prognostically important, as pre-excitation syndrome, have no prognostic impact in a community setting(10). For the other side, the risk of dying for a person with right bundle branch block (BBB) is almost as high as with a left BBB(11), the latter being considered a much stronger marker of risk in the general cardiology practice. The CODE (Clinical Outcomes in Digital Electrocardiology) study is a

large database that comprises all ECGs performed mostly at primary health care facilities by the Telehealth Network of Minas Gerais, Brazil, from 2010 to 17(12). The ECG database was linked to the national mortality information system and can provide epidemiological information in a population that is representative of the general population. Thus, in the present study, we aim to describe AVB prevalence, its risk factors and, mainly, evaluate the association between AVB with overall mortality in this large primary care Brazilian cohort.

Methods

We conducted a retrospective study using a database of digital ECGs from the Telehealth Network of Minas Gerais (TNMG)(13). This public Brazilian telehealth system has performed more than 5 million ECGs since its inception, in 2006, and is responsible for the ECG report of more than 1000 municipalities in Brazil.

For this study, we analyzed the CODE dataset(12)(14), which comprises all valid ECGs performed in patients over 16 years old by the TNMG from 2010 to 2017. Exams without valid tracings or with technical problems were excluded. In patients who underwent more than one ECG, only the first exam was analyzed. ECGs were performed by the local primary care professional, using digital electrocardiographs by Tecnologia Eletrônica Brasileira model ECGPC (São Paulo, Brazil) or Micromed Biotecnologia model ErgoPC 13 (Brasilia, Brazil).

Clinical data (age, sex and comorbidities) were collected using a standardized questionnaire. Clinical conditions included hypertension, diabetes, self-reported smoking, Chagas disease, previous myocardial infarction and chronic obstructive pulmonary disease.

A specific software, developed in-house, was capable of capturing ECG tracing, uploading the ECG and the patient‘s clinical history and, then, sent to the TNMG analysis center through the internet. The clinical information, ECGs tracings and reports were stored in a specific database. The ECG reports were done in a free text model by cardiologists and, also, automatically interpret and coded into Glasgow and Minnesota codes by the Glasgow 12-lead ECG analysis program (release 28.4.1, issued on June 16th 2009) (15).

The medical reports were performed by a team of fourteen trained cardiologists using standardized criteria. Each ECG was interpreted by only one cardiologist. The

electrocardiographic diagnosis of AVB was divided into: first-degree AVB, second-degree Mobitz type I AVB, second-degree Mobitz type II, 2:1 AVB, high-degree AVB and third-degree AVB(3) (Table 1). In this study, we did not included Mobitz type II because of the low prevalence (seven cases) and high-degree AVB (six cases) was grouped into third-degree AVB for the analysis.

Table 1- Definition and classification of atrioventricular block (3)

Type of AVB	Definition
First-degree	P waves associated with 1:1 atrioventricular conduction and a PR interval >200 ms
Second-degree Mobitz type I	P waves with a constant rate (<100 bpm) with a periodic single nonconducted P wave associated with P waves before and after the nonconducted P wave with inconstant PR intervals
Second-degree Mobitz type II	P waves with a constant rate (< 100 bpm) with a periodic single nonconducted P wave associated with other P waves before and after the nonconducted P wave with constant PR intervals (excluding 2:1 atrioventricular block)
2:1	P waves with a constant rate (or near constant rate because of ventriculophasic sinus arrhythmia) rate (<100 bpm) where every other P wave conducts to the ventricles
High-degree	≥2 consecutive P waves at a constant physiologic rate that do not conduct to the ventricles with evidence for some atrioventricular conduction
Third-degree	No evidence of atrioventricular conduction

The ECG medical report was done as an unorganized free text. In order to recognize AVB diagnosis among these million reports, hierarchical free-text machine learning was used. First, the text was preprocessed by removing stop-words and generating n-grams. Then, we used the classification model called Lazy Associative Classifier(16), which was built with a 2800-sample dictionary manually created by specialists based on text from real diagnoses. The final report was obtained by imputing

the Lazy Associative Classifier results to a decision tree for class disambiguation. The decision tree was trained using the original dataset. The classification model was tested on 4557 medical reports manually labeled by two cardiologists with 99% accuracy, 100% positive predictive value and 99% sensibility(17).

Electrocardiographic diagnosis of AVB was considered automatically when there was agreement between cardiologist report and automatic report from Glasgow or Minnesota code. In the cases where there were discordances between medical report and one of the automatic programs, a manual revision of 9038 ECGs was done by trained staff. Those where AVB were diagnosed only by one of the automatic systems were not considered (Figure 1). The control group was composed of patients without any type of AVB.

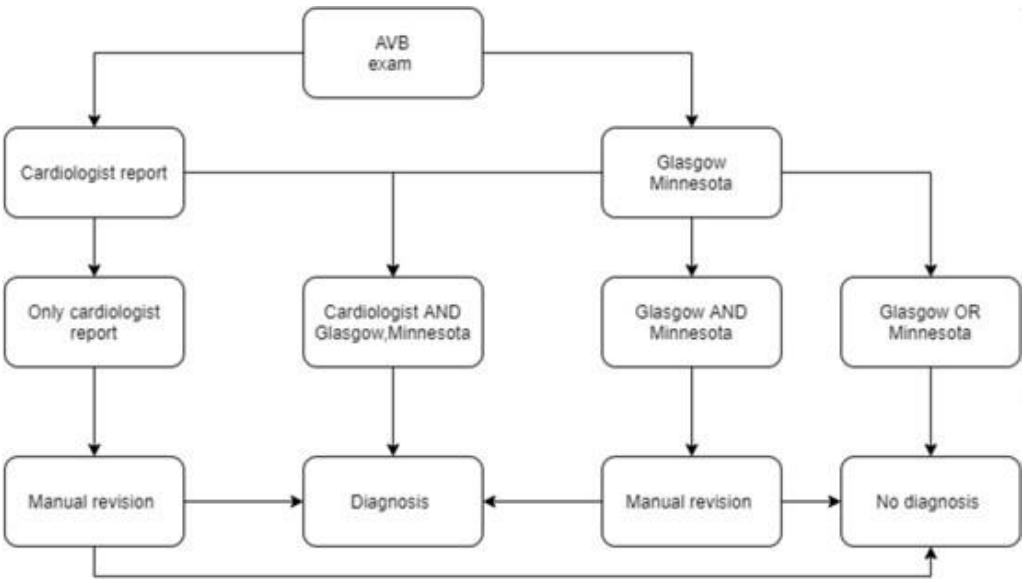

Figure 1- Diagram for atrioventricular block diagnosis in the ECG database

The electronic cohort was obtained linking data from the ECG exams (name, sex, date of birth, city of residence) and those from the national mortality information system(12), using standard probabilistic linkage methods (FRIL: Fine- grained record linkage software, v.2.1.5, Atlanta, GA)(12)(18).

R program (version 3.4.3, Vienna, Austria) was used for statistical analysis. Categorical data were reported as counts and percentages; continuous variables were reported as mean and SD or median (25th, 75th percentiles), as appropriated. The end point was all-cause mortality that included all International Classification of Diseases codes in the medical certification of cause of the death. The Kaplan-Meier method was used to estimate the survival curves for all causes of death. We used the likelihood ratio test (LRT) to adjust data for the best parametric model, since the proportional assumption for the Cox regression model was violated. In the LRT, the generalized model, represented by the generalized Gamma regression model, was compared with the other models of interest (Weibull and Log-normal). We chose to work with the log-normal model. Relative survival rate (RS) was used as the measure of association, with confidence interval of 95%. RS < 1 means higher risk of mortality and RS > 1 lower risk. Two-tailed P-value of 0.05 was considered statistically significant. This study was approved by the Research Ethics Committee of the Federal University of Minas Gerais.

Results

A total of 1,557,901 patients were included: 40.23% men with a mean age of 51.67 (SD+ -17.58) years. In a mean follow-up of 3.7 years, the mortality rate was 3.35%. The AV block prevalence was 1.38% (21,538); 1.32% (20,644) corresponding to first-degree AV block, 0.02% (273) to second and 0.04% (621) to third-degree AV block. Among these 273 second-degree AVB, 212 were Mobitz type I and 61 were 2:1. The clinical conditions of all patients are described in Table 2.

Table 2- Baseline data of the patients, according to the presence of atrioventricular block and respective degree

	Without AVB n=1,536,363	First-degree AVB n=20,644	Adjusted OR*	Second-degree AVB n=273	Adjusted OR*	Third-degree AVB n=621	Adjusted OR*
Age (years)	51.5 (17.5)	64.9 (16.9)	-	61.7 (19.8)	-	66.6 (17.5)	-
Male sex	615,097 (40)	11,176 (54.1)	-	164 (60.1)	-	286 (46.1)	-
Hypertension	492.488 (32.1)	9370 (45.4)	1.23 (1.19-1.26)	100 (36.6)	0.89 (0.69-1.15)	298 (48.0)	1.18 (1.01-1.39)
Diabetes	100,844 (6.6)	1826 (8.8)	1.10 (1.05-1.15)	18 (6.6)	0.87 (0.52-1.36)	55 (8.9)	1.05 (0.78-1.37)
Current smoking	107,346 (7.0)	1384 (6.7)	0.90 (0.85-0.95)	20 (7.3)	0.93 (0.57-1.43)	51 (8.2)	1.21 (0.90-1.60)
Chagas disease	33,134 (2.2)	1336 (6.5)	2.76 (2.60-2.92)	35 (12.8)	6.04 (4.16-8.50)	81 (13.0)	5.75 (4.52-7.23)
Myocardial infarction	11,286 (0.7)	304 (1.5)	1.48 (1.31-1.66)	0 (0.0)	-	11 (1.8)	1.80 (0.93-3.10)
COPD	11,029 (0.7)	231 (1.1)	1.14 (1.00-1.30)	0 (0.0)	-	4 (0.6)	0.64 (0.20-1.49)

Data are present as mean (SD) or number (%)

AVB, atrioventricular block; COPD, chronic obstructive pulmonary disease; OR odds ratio

*age, sex, hypertension, diabetes, current smoking, Chagas disease and chronic obstructive pulmonary disease

After adjustment for sex, age and clinical conditions, patients with first-degree, second and third- degree AVB were associated with 24%,55% and 64% lower survival rate when compared to control, respectively (Figure 2). In the survival analysis divided by subtype of AVB, only the second-degree Mobitz type I was not associated with higher mortality. Patients with 2:1 AVB had 79% lower survival rate than the control group while third-degree AVB had 64% (Table 3; Figure 2).

Table 3- Prognostic value of patients with subtypes of atrioventricular block

	RS (95% CI)		
Type of AVB	Model 1: Unadjusted	Model 2: Adjusted for age and sex	Model 3: Adjusted for clinical variables*
First-degree	0.24(0.23-0.26)	0.73(0.69-0.78)	0.76(0.71-0.81)
Mobitz I	0.26(0.13-0.50)	0.63(0.33-1.20)	0.65 (0.34-1.24)
2:1	0.05(0.02-0.13)	0.20(0.08-0,50)	0.21(0.09-0.52)
Third-degree	0.11(0.08-0.15)	0.34(0.25-0.46)	0.36(0.26-0.49)

AVB, atrioventricular block; RS, relative survival rate; CI, confidence interval

*age, sex, hypertension, diabetes, current smoking, Chagas disease and chronic obstructive pulmonary disease

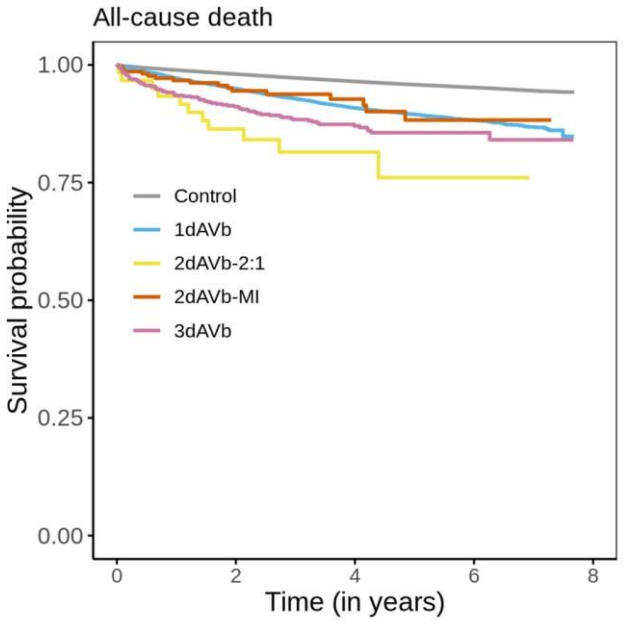

Figure 2- Kaplan-Meier survival curves, according to the subtype of atrioventricular block

Discussion

In this large electronic cohort with more than one million patients, AVB was associated with higher risk of overall mortality. Regarding the type of AVB, only Mobitz type I did not have an increased risk of mortality, comparing to the control group.

In patients with structural heart disease, first-degree AVB has been described as a risk factor for adverse outcome(19)(20). On the other hand, previous longitudinal studies in the general population that included, mainly, young and middle-age men founded that prolonged PR interval has a benign course(21)(22)(23). We should highlight that this data came from specific population with limited surveillance and a relative low sample of patients with AVB. More recently, a publication from the Framingham cohort(4) changed this paradigm. After twenty years of follow up, PR prolongation was associated with increased risk of atrial fibrillation (AF) (HR, 2.06; 95% CI 1.36-3.12;p<0.001), pacemaker implantation (HR, 2.89; 95% CI 1.83-4.57; p<0.001) and death (HR, 1.44; 95% CI 1.09-1.91;p=0.01)(4). A large Danish ECG study with 288,181 patients confirmed the higher risk for AF associated with the presence of first AVB(24).

In our population, a 24% reduction in the survival rate of patients with PR > 200 ms, after adjustment for age, sex and clinical conditions were found, contrary to previous study in the Finnish population(25). Some differences between these cohorts must be pointed out. The Brazilian was older (mean age 51.7 versus 44 years) and also included elderly patients. We analyzed about 1.5 million ECG versus ten thousand. Chagas disease was relatively prevalent with strong association with the presence of AVB, independently of the degree. The social differences between the two countries might also have contributed. Accesses to public health services and population education are completely unequal in the low and middle income countries and may have prognostic impact in the population(26).

It is well established that irreversible Mobitz type II, high and third-degree AVB are indications of permanent pacing even in asymptomatic patients(3). Their association with mortality is expected(9), since AV conduction injury is more severe and heart disease are often related(3). The prognosis in the 2:1 AVB is intimately related to the site of the AVB: nodal or infranodal(3). In the present study, 2:1 AVB in the 12-lead ECG was associated with 79% reduction of the relative survival, probably, indicating an infranodal block. The Mobitz type I AVB, on the other hand, was not associated with higher mortality in our cohort.

The Mobitz type I AVB has frequently a benign prognosis, especially in young patients without cardiac disease(27). It can be a vagal mediated AVB that does not have an anatomical involvement of AV conduction(28) and, therefore, does not progress to a high-degree AVB. In older patients, the natural history can be different and they might benefit from a permanent pacemaker(29). We did not perform a sub analysis in elderly patients and the presence of symptoms is unknown.

Patients with cardiovascular emergences often seek health assistance in primary care units, especially in small and remote counties. Tele-electrocardiography service has an important role in this setting, mainly for recognizing ECG abnormalities misdiagnosed by the local physician that can be life threatening(30). In our service, second degree AVB was statistically higher in the ECGs assigned as elective that in those with emergency priority(30). The patient´s outcome could change with the early referral to the hospital and, consequently, pacemaker implantation(31). Hospitalization data was not available for our entirely cohort and, therefore, was not included in this paper. Nonetheless, further work in this field is planned to evaluate the patient journey in our healthcare system from the ECG diagnosis with AVB.

Limitations:

Our study has limitations. The clinical data was self-reported and, thus, might have been underreported. The software Lazy Associated Classificator used for ECG report classification has good accuracy, sensibility and positive predictive value, but can have errors. In order to minimize this problem, we included the automatic classification of Glasgow and Minnesota to the diagnostic algorithm. Furthermore, manual revision was done in more than 9,000 ECG to confirm the presence of AVB. The probabilistic linkage also has some issues as a less than perfect sensitivity and the possibility of false pairs. Therefore, we defined a high cut off point for true pairs and made a manually revision for the doubtful cases. We still do not have information on symptoms or hospitalization data, but data from pacemaker procedure in each group will soon be available for analysis and future work has been planned in this matter.

Nevertheless, our study brings new data on AVB prognosis, as evaluates a Latin Population from primary care center with more than one million patients. Our findings are consistent and might be a useful tool to direct public health policies and funding resources.

Conclusion:

The presence of AVB was associated with an increased risk of overall mortality in the TNMG population. In patients with second and third-degree AVB, only those with Mobitz type I did not have a higher risk of mortality.

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6.3. ARTIGO 3

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Ventricular pre-excitation in primary care patients: evaluation of the risk of mortality

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Abstract

Background: Ventricular pre-excitation is characterized by the presence of atrioventricular accessory pathways, predisposing to arrhythmias. Although it is well established that risk stratification in symptomatic patients should be invasive, there is a lack of evidence of the benefit in asymptomatics. **Objective:** Evaluate ventricular pre-excitation in the electrocardiogram (ECG) as a risk factor for overall mortality in patients of Telehealth Network of Minas Gerais (TNMG), Brazil. **Methods:** This observational study was developed with the database of digital ECGs (2010-2017) from TNMG. The electronic cohort was obtained by linking data from ECG exams and those from national mortality information system. Only the first ECG was considered. Clinical data were self-reported, and ECGs were interpreted manually by cardiologists and automatically by the Glasgow University Interpreter software. Hazard ratio (HR) for mortality was estimated using weighted Cox regression. **Results:** 1,665,667 patients were included (median age 50 [Q1:34; Q3:63] years; 41.4% were male). In a mean follow-up of 3.7 years, the overall mortality rate was 3.1%. The prevalence of ventricular pre-excitation was 0.07%. In multivariate analysis, adjusting for sex and age, ventricular pre-excitation was not associated with an increased risk of mortality (HR 1.41, 95% CI 0.56-3.57; p=0.47) when compared to the whole sample or to patients with normal ECG (HR 1.41, 95% CI 0.53-4.36; p=0.43). In a sub analysis on accessory pathway location, there was no evidence of a higher risk of death related to any location. **Conclusion:** Ventricular pre-excitation was not associated with an increased risk of mortality in a primary care cohort.

Keywords: ventricular pre-excitation, mortality, electrocardiogram, primary care.

Introduction

Ventricular pre-excitation occurs due to the presence of one or more atrioventricular conduction pathways, which are manifested on the electrocardiogram (ECG) by a short PR interval, delta wave, and QRS complex enlargement(1). The prevalence in the general population is about 0.1 to 0.3%(2). The ECG pattern associated with palpitations or syncope establishes the diagnosis of Wolf-Parkinson-White (WPW) syndrome.

Patients with WPW syndrome have increased risk of ventricular arrhythmia with an estimated risk of sudden cardiac death (SCD) of 0.25% per year or 3% to 4% throughout life(3). It is well established that symptomatic patients should undergo an electrophysiological (EP) study and catheter ablation of the accessory pathway(4). In asymptomatic patients, evidence is limited if the risk stratification for SCD should be invasive or not(5). The randomized studies had small sample size (6) with most of the population from tertiary hospitals (7)(8).

The natural history of ventricular pre-excitation has not been fully evaluated(9). Few cohorts with a small number of patients showed the benign prognosis of ventricular pre-excitation(3)(10). More recently, a study with 328,638 primary care patients showed no association between mortality and ventricular pre-excitation, but a higher risk of developing atrial fibrillation and heart failure(8). The literature still lacks studies with large ECG databases from the general population(9). Therefore, our aim is to evaluate the presence of ventricular pre-excitation in the ECG as a risk factor for overall mortality in a Brazilian primary care population.

Methods

We conducted an observational retrospective study using a database of digital ECGs from the Telehealth Network of Minas Gerais (TNMG)(11). This public Brazilian telehealth system has performed more than 4 million ECGs since its inception, in 2006, and is responsible for the ECG report of more than 1000 municipalities in Brazil.

All valid ECGs performed by the TNMG from 2010 to 2017 were assessed. The majority of patients (79%) underwent ECG in outpatient setting. Exams without valid tracings or with technical problems were excluded. In patients who underwent more than one ECG, only the first exam was analyzed. ECGs were performed by the local primary care professional, using digital electrocardiographs by Tecnologia Eletrônica Brasileira model ECGPC (São Paulo, Brazil) or Micromed Biotecnologia model ErgoPC 13 (Brasilia, Brazil).

Clinical data (age, sex and comorbidities) were collected using a standardized questionnaire. Clinical conditions included self-reported smoking, hypertension, diabetes, dyslipidemia, Chagas disease, previous myocardial infarction and chronic obstructive pulmonary disease. Data from catheter ablation was not available.

A specific software, developed in-house, was capable of capturing ECG tracing, uploading the ECG and the patient‘s clinical history and, then, sent to the TNMG analysis center through the internet. The clinical information, ECGs tracings and reports were stored in a specific database. For the purpose of the present study, the Glasgow 12-lead ECG analysis program (release 28.4.1, issued on June 16th 2009) was used to automatically interpret all ECGs available in the database, exporting the diagnosis, codified by both Glasgow and Minnesota codes(12).

ECGs were analyzed by a team of fourteen trained cardiologists using standardized criteria(1). Each ECG was interpreted by only one cardiologist. The electrocardiographic

diagnosis of ventricular pre-excitation was considered in the presence of short PR interval, delta wave and QRS complex prolongation(1).

The ECG medical report was done as an unorganized free text. In order to recognize ventricular pre-excitation diagnosis among these million reports, a hierarchical free-text machine learning was used. First, the text was preprocessed by removing stop-words and generating n-grams. Then, we used the classification model called Lazy Associative Classifier(13),which was built with a 2800-sample dictionary manually created by specialists based on text from real diagnoses. The final report was obtained by imputing the Lazy Associative Classifier results to a decision tree for class disambiguation. The decision tree was trained using the original dataset. The classification model was tested on 4557 medical reports manually labeled by two cardiologists with 99% accuracy, 100% positive predictive value and 99% sensitivity.

All ECGs with reported ventricular pre-excitation by the cardiologists or by two automatic systems (Minnesota and Glasgow) were manually reviewed by one physician. If there was disagreement, a clinical electrophysiologist made the final decision. The exams with ventricular pre-excitation reported only by one of the automatic systems were not considered. For the classification of the accessory pathway location, the algorithm provided by D'Ávila et al.(14) was used. The locations of the accessory pathway were classified left lateral, left posteroseptal, right posteroseptal, right lateral, anteroseptal and mid-septal. All classifications were done by three physicians and reviewed by a clinical electrophysiologist. The normal ECG definition was an ECG reported as normal by the cardiologist with all normal automatic ECG measures by the Glasgow University Software.

The electronic cohort was obtained linking data from the ECG exams (name, sex, date of birth, city of residence) and those from the national mortality information system, using standard probabilistic linkage methods (FRIL: Fine- grained record linkage software,

v.2.1.5, Atlanta, GA). R program (version 3.4.3, Vienna, Austria) was used for statistical analysis. Categorical data were reported as counts and percentages; continuous variables were reported as mean and SD or median (25th, 75th percentiles), as appropriate. The Kaplan-Meier method was used to estimate the survival curves for all causes of death. Cox regression adjusted by age and sex was used to assess the association between ventricular pre-excitation and mortality. The end point was all-cause mortality that included all International Classification of Diseases codes in the medical certification of cause of the death. Regarding the accessory pathway location, a subgroup analysis was also performed. Due the presence of non-proportional hazards the model coefficients were obtained using a weighted estimation and average hazard ratios were reported. Confidence interval of 95% was used. Two-tailed P-value of 0.05 was considered statistically significant. This study was approved by the Research Ethics Committee of the Federal University of Minas Gerais.

Results

From a dataset of 1,773,689 patients, 1,666,778 (94%) underwent a valid ECG recording during 2010 to 2017 and, therefore, were included. The median age was 50 [Q1:34; Q3:63] years; 41.4% were male. The prevalence of ventricular pre-excitation was 0.07%. The overall mortality rate was 3.06% in a mean follow-up of 3.7 years.

Ventricular pre-excitation patients had a median age of 38 [Q1:27.5; Q3:51] years, significantly younger than those without ventricular pre-excitation, with 53.2% male. Hypertension, diabetes Mellitus and Chagas disease were more prevalent in patients without pre-excitation. Abnormalities in the ECG measures (short PR interval, longer duration of the QRS complex and QTc interval) were more frequent in ventricular pre-excitation, as expected (Table 1). Ventricular pre-excitation pathways were divided into midseptal, left lateral, anteroseptal, left posteroseptal, right posteroseptal and right lateral (Table 2).

Table 1 – Baseline data by prevalence of ventricular pre-excitation

Variables	Without ventricular pre-excitation (n=1.539.206)	With ventricular pre-excitation (n=1.090)	p Value
Age (Years)*	52(38-65)	39(28-51)	<0.001
Sex:			
Female	59,8%	46.9%	Ref.
Male	40,2%	53.1%	<0.001
Hypertension	31.7%	22.6%	<0.001
DM	6.5%	3.8%	<0.001
Current Smoking	7.0%	6.5%	0.56
Chagas disease	2.2%	1.2%	0.03
MI	0.7%	0.8%	0.89
COPD	0.7%	0.4%	0.22
Glasgow Measures+:			
Heart rate (bpm)	70 (62-80)	69 (60-78)	<0.001
PR interval (ms)	150 (136-168)	110 (98-120)	<0.001
QRS interval (ms)	92 (86-100)	128 (111-140)	<0.001
QTc interval (ms)	417 (404-432)	441 (427-455)	<0.001

+median; first quartile; third quartile

DM diabetes mellitus; MI previous myocardial infarction; COPD chronic obstructive pulmonary disease; bpm beats per minute; ms milliseconds.

Table 2 - Distribution of the accessory pathways location in patients with ventricular pre-excitation

Accessory pathway	Frequency, n (%)
MS	381 (34.8)
LL	194 (17.7)
AS	184 (16.9)
LPS	160 (14.6)
RPS	97 (8.8)
RL	79 (7.2)

AS anteroseptal; MS midseptal; LL left lateral; LPS left posteroseptal; RPS right posteroseptal; RL right lateral

In a multivariate analysis, adjusted by sex and age, the presence of ventricular pre-excitation in the ECG was not associated with an increased mortality when compared to the population without pre-excitation (HR 1.41, 95% CI 0.56-3.57; p=0.47). Compared with patients with a normal ECG (n=695,011), ventricular pre-excitation was not a risk factor for overall mortality (HR 1.41, 95% CI 0.53-4.36; p=0.43) (Figure 1). No interaction was detected with age over 65 years (HR 1.13, 95% CI 0.34-3.75; p=0.84).

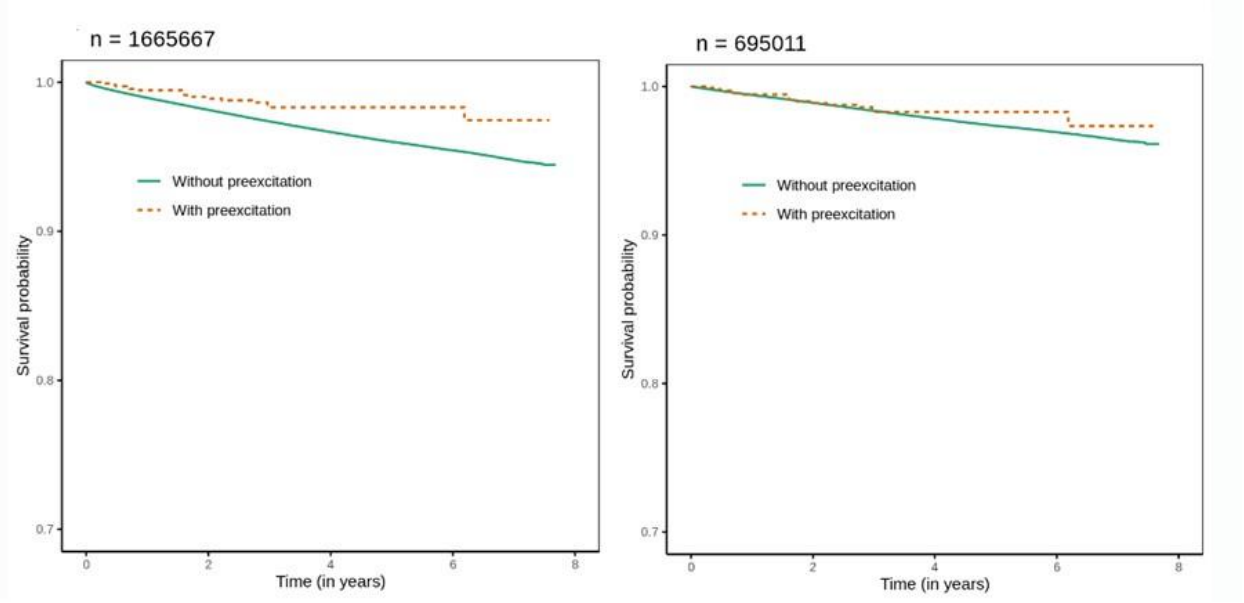

Figure 1- Kaplan-Meier curves for overall mortality in ventricular pre-excitation

In the subgroup analysis by accessory pathway location for mortality, we had to group the pathways into left side (left lateral and left posteroseptal), posteroseptal (right posteroseptal and mid-septal) and anteroseptal. The right lateral pathway was not included because there was no event in this subgroup. We did not find any difference in mortality compared to all patients without pre-excitation and patients with normal ECG (Table 3).

Table 3- Hazard ratio for mortality, adjusted for age and sex, in patients with pre-excitation, according to the accessory pathway location

Accessory pathway location	All patients (HR CI 95%)	p-value	Patients with normal ECG (HR CI 95%)	p-value
AS	0.87 (0.22-3.50)	0.84	1.06 (0.26-4.26)	0.93
LE	1.34 (0.70-2.60)	0.37	1.67 (0.86-3.22)	0.13
PS	0.78 (0.32-1.90)	0.58	0.97 (0.40-2.33)	0.94

AS anteroseptal; LE left side; PS posteroseptal; HR, hazard ratio; CI, confidence interval

Discussion

Our study showed that ventricular pre-excitation was not associated with higher risk of overall mortality in a primary care population in a mean follow up of 3.7 years, even when compared to patients with normal ECG. The accessory pathway location was not related to an increased risk in the mortality.

Our prevalence of ventricular pre-excitation was similar to the Danish primary care population(8). In a study with specific populations such as the United States Air Force, the prevalence was probably higher because there were more younger healthy male patients (2). The higher prevalence in male sex was also observed in others studies (3,8).

The prevalence of comorbidities (hypertension, diabetes and Chagas disease) was lower in pre-excitation patients, as expected, since the population is younger(3,8). The other comorbidities did not have statistical differences between the two groups, probably, because the clinical conditions are self-reported with an underestimation of their real prevalence.

Midseptal pathway was the most frequent in our population which differs from other studies(8). The algorithm used for classification of the pathways in the Danish population was described by Fox et al(15) and does not classify in midseptal and left posteroseptal. Therefore, their left lateral is the left lateral and left posteroseptal classified by the D'Ávila algorithm(14) and their posteroseptal includes midseptal and right posteroseptal (Figure 2). Considering the difference in the classification of the algorithms, the findings are similar and consistent with other published studies(8,16). Some ECG may have an incomplete degree of pre-excitation which difficult the classification and predispose to disagreement. It is also important to highlight that accessory pathway location was only evaluated by the 12 lead ECG and not confirmed by EP study.

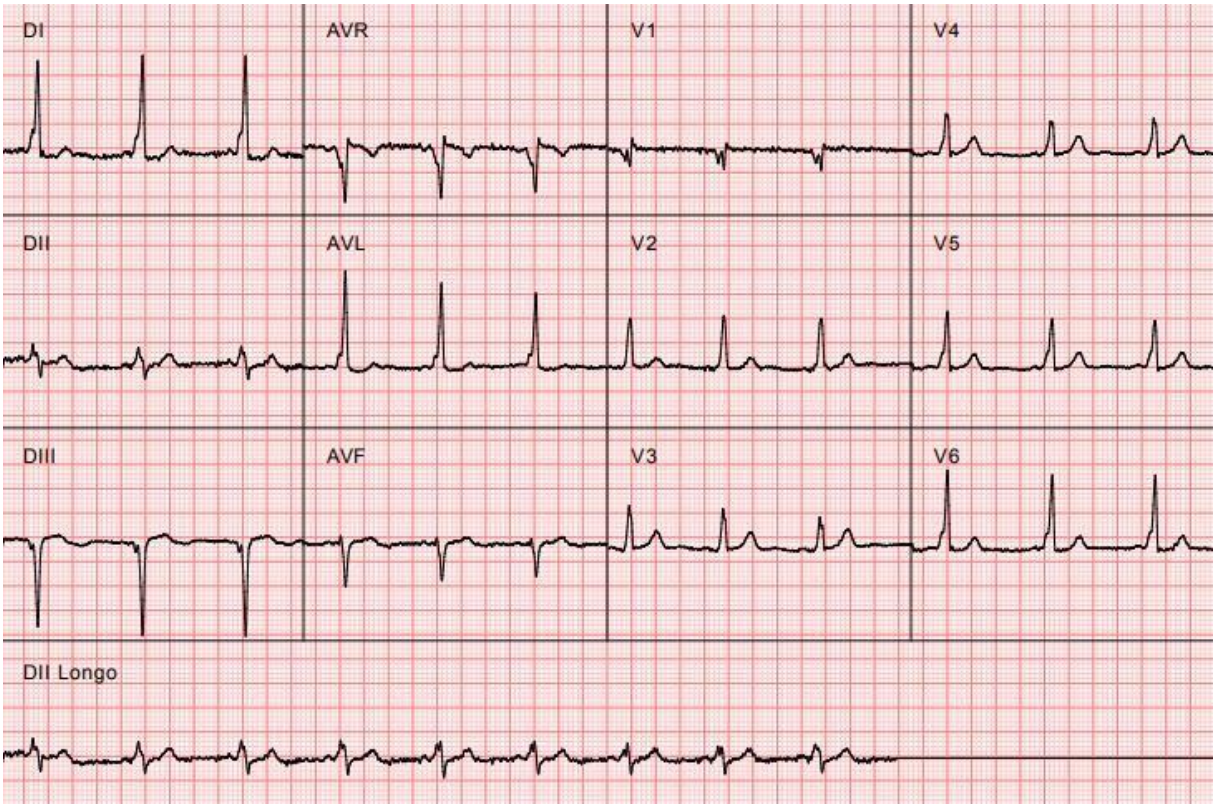

Figure 2- Midseptal preexcitation by D'Ávila algorithm vs. posteroseptal by Fox et al algorithm

The good prognosis of ventricular pre-excitation has been already reported(3)(8)(10)(17), especially in asymptomatic patients(3) and a long anterograde effective refractory period of the accessory pathway and no inducibility at baseline in the EP study(17). In the Danish population, there was a higher risk of developing atrial fibrillation and heart failure and a higher risk of death for patients with ventricular pre-excitation over 65 years(8). We did not find any interaction with mortality in patients over 65 years. Other cardiac events, such as arrhythmia, heart failure and syncope, were not evaluated in the present study.

The present results came from an electronic cohort with millions of patients (18) that have already shown the prognosis value of other ECG abnormalities (19)(20). As our findings are consistent with the literature, it might be reasonable to be conservative in

asymptomatic adults patients, especially when the access to tertiary health services is difficult and the resources are limited in the public health system.

Limitations:

We have evaluated databases that are subject to errors of filing and information. Our clinical conditions were self-reported, which may have underestimated their prevalence. Data from EP studies were not available, thus we do not have an information if the patient underwent a catheter ablation.

We always analyzed the first ECG of all patients. Since there is no structured follow-up of these patients, we do not have information on the repeated ECGs Therefore, patients with intermittent pre-excitation were not identified. Our population is mainly composed by adults (median age 39 years); interpretation of these results should not be extrapolated in the pediatric population. The mean follow up was relative short, therefore, low long term risk of death cannot be assured.

The LAC software, used to classify the electrocardiographic report in free text, has good accuracy, sensitivity and predictive value, but it is not free of errors (13).

As the study involves a large electronic cohort with millions of patients, we believe that the limitations presented do not affect our findings. This is the first study with Brazilian primary health care patients that evaluated the prognostic value of ventricular pre-excitation in the ECG.

Conclusion

The presence of ventricular pre-excitation in the ECG was not associated with an increased risk of mortality in a Brazilian primary care population.

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6.4. ARTIGO 4

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Deep neural network estimated electrocardiographic-age as a mortality predictor

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Abstract:

The electrocardiogram (ECG) is the most commonly used exam for the evaluation of cardiovascular diseases. Here we propose that the age predicted by artificial intelligence (AI) from the raw ECG (ECG-age) can be a measure of cardiovascular health. A deep neural network is trained to predict a patient's age from the 12-lead ECG in the CODE study cohort (n=1,558,415 patients). On a 15% hold-out split, patients with ECG-age more than 8 years greater than the chronological age have a higher mortality rate (hazard ratio (HR) 1.79, p<0.001), whereas those with ECG-age more than 8 years smaller, have a lower mortality rate (HR 0.78, p<0.001). Similar results are obtained in the external cohorts ELSA-Brasil (n=14,236) and SaMi-Trop (n=1,631). Moreover, even for apparent normal ECGs, the predicted ECG-age gap from the chronological age remains a statistically significant risk predictor. These results show that the AI-enabled analysis of the ECG can add prognostic information.

Keywords: Biological aging, electrocardiogram, mortality prediction, artificial intelligence.

Introduction

The electrocardiogram (ECG) is the most commonly used exam for the screening and evaluation of cardiovascular diseases. Computerized, rule-based, ECG interpretation was developed to facilitate medical research and clinical practice. However, the limited accuracy of these methods has limited their application[1,2]. In this context, deep neural networks (DNNs) are a promising machine learning approach for the automated analysis of the ECG and have achieved unprecedented performance in initial studies[3,4].

DNNs present a paradigm shift from classical ECG automated analysis methods. Classical methods use signal processing techniques to extract the measurements, wavelengths and detect abnormal beats from the ECG signal and then use the extracted information as input features to a classifier[5]. DNN-based ECG analysis, on the other hand, is based on an "end-to-end" approach, for which the raw signal is used as an input to the classifier, which learns to extract the features by itself [3,4].

Unlike the traditional methods, features learned by end-to-end ECG automated analysis methods do not necessarily have an interpretation rooted in electrocardiographic knowledge. If this paradigm introduces new challenges regarding model interpretability[6] and out-of-distribution robustness[7], it also introduces new possibilities when it comes to applications. Examples that go beyond traditional electrocardiography and have been achieved using end-to-end approaches include: predicting the risk of death from the ECG [8]; identifying patients who will develop atrial fibrillation from a previous ECG taken during sinus rhythm[9]; and screening for cardiac contractile dysfunction using only the 12-lead ECG [10]. This suggests that end-to-end models might be able to identify additional markers that, in turn, might be practical and useful tools in cardiovascular disease prediction.

In this context, we turn to the use of machine learning algorithms to infer age from ECG tracings[11,12]. Previous studies have shown that the age estimated from the ECG (the ECG-age) is related to cardiovascular health[11,12]: The ECG-age, calculated using a Bayesian model in 5-minutes ECGs, tended to be close to the chronological age in healthy non-athletes, whereas most subjects with risk factors or proven heart diseases had a predicted ECG-age that was higher than their chronological age[11]; in another study, patients with a DNN-predicted age that exceeded the chronologic age by 7 or more years presented a higher frequency of low ejection fraction, hypertension, and coronary disease[12]. More recently, ECG-derived age has also been related to vascular aging, measured by peripheral endothelial dysfunction[13].

Biological aging refers to the decline in tissue/organismal function, whereas chronological aging simply indicates the time passed since birth[14]. In normally aging individuals, chronological and biological ages are the same. Biological aging, however, is affected by lifestyle, environmental factors, inheritable and acquired conditions, and diseases. Accelerated biological aging points to the decline of tissue/organismal function at a faster rate than the average, and hence associated with the risk of a premature death[14]. Most available biomarkers of biological age measure a specific aspect of aging, like molecular and cellular biomarkers, and functional and structural vascular parameters[14]. Multiple exams and composite scores are often needed, adding cost, risk, and complexity to the evaluation. ECG exams are low-cost and widely available, being part of the routine evaluation of many patients in both primary and specialized care. Thus, if ECG can provide an accurate estimate of the biological age it can be potentially useful in clinical practise.

We build on the hypothesis that an AI model exposed to many ECG exams with the task of predicting the age might learn to capture, on average, how aging affects the ECG

exam. Age is a risk factor for cardiac diseases that affects ECG measurements and the likelihood of having an ECG with a higher incidence of abnormalities[15,16]. Hence, here we study the possibility of using this AI predicted ECG-age as an indicator of cardiovascular health. We refer to this age predicted by the AI model from the raw 12-lead ECG tracing as predicted ECG-age, or just ECG-age, and, to contrast that, we refer to the patient age as chronological age.

In this paper, we demonstrate that this AI predicted ECG-age is a potentially useful tool in the assessment of the risk of death in the general population. We developed, in the CODE Study cohort[17], a DNN-based age-prediction model and assessed if the difference between predicted ECG-age and chronological age is a predictor of overall mortality. The model is validated in two external cohorts, ELSA-Brasil[18], of Brazilian public servants, and SaMi-Trop[19], of Chagas disease patients. Furthermore, we tested if the predictive value remains significant after controlling for the presence of cardiovascular risk factors and for subjects with normal ECGs. We sought to determine whether it can be used as a prognostic marker in the general population. Finally, we also undertook an exploratory analysis to investigate mechanisms that are involved in ECG-age prediction, looking at the main components used during the classification. This is done both by analysing the model sensitivity to changes in the ECG signal and by the manual review of the ECGs and the corresponding predicted ECG-age by trained cardiologists.

Results

Deep neural network age-predictor model

We used the CODE Study cohort[17] to develop a DNN capable of predicting the patient's age from the raw ECG tracing. The dataset consists of ECG records from 1,558,415 patients of 811 counties in the state of Minas Gerais (Brazil) collected by the Telehealth Network of Minas Gerais (TNMG). Patients were divided into 85-15% splits with the 85% split being used to develop the model (see Methods).

The model is evaluated in 3 different cohorts, unseen by the DNN model during its development, the 15% hold-out split described above, which will be referred to as the CODE-15% cohort (with 218,169 participants), the ELSA-Brasil (with 14,236 participants), and the SaMi-Trop cohorts (with 1,631 participants). Table 1 summarizes the baseline characteristics for each of the cohorts including median follow-up and number of events. Compared to the CODE-15% cohort, mean age, the prevalence of cardiovascular risk factors, and previous myocardial infarction were higher in both ELSA-Brasil and SaMi-Trop cohorts. The frequency of events was the highest in the SaMi-Trop cohort, composed of Chagas disease patients, many with chronic cardiomyopathy.

We used the DNN architecture known as the residual network[20] to perform the task. The architecture has been successfully used for ECG abnormality detection in previous work[3,4]. The DNN mean absolute error (MAE) in the age prediction task is 8.38 (with standard deviation, s.d., 7.00), 8.44 (s.d. 6.19) and 10.04 (s.d. 7.76) for the CODE-15%, ELSA-Brasil, SaMi-Trop, respectively. Figure 1 shows the relation between predicted ECG-age and chronological age for all the patients in the cohorts.

In the following sections, we try to establish the prognostic relevance of the ECG-age. We perform regression analyses that use the ECG-age as an input variable. In these analyses we always use the CODE-15% cohort for deriving the statistics and the ELSA-Brasil and SaMi-Trop for validating them.

Electrocardiographic-age as a mortality predictor

We try to establish the relevance of ECG-age as a predictor of mortality. We divided the patients into three groups, based on differences between predicted ECG-age and chronological age: a) those with ECG-age more than 8 years greater than the chronological age; b) those with ECG-age within a range of 8 years from their chronological age; and, c) those with ECG-age more than 8 years smaller than the chronological age. The MAE in the CODE dataset is approximately 8 years, which motivates our choice for the thresholds used. That is, when the predicted ECG-age deviates from the chronological age by more than the mean deviation found in the derivation cohort we classify into group (a) if the deviation is positive, and into group (c), if it is negative. Experiments with alternative choices of threshold yield qualitatively similar results.

The risk of death for these three groups, expressed by their hazard ratios (HR), is shown in Table 2, together with the 95% confidence intervals (CI). We fit a Cox model, adjusted for age and sex, in the CODE-15% cohort. The adjusted survival curves for this model are presented in Figure 2. This model indicates that participants with an estimated ECG-age of more than 8 years greater than the chronological age had higher mortality risk (HR 1.79, 95%CI 1.69-1.90; $p<0.001$). On the other hand, those with an estimated ECG-age of more than 8 years smaller than the chronological age had a lower mortality risk (HR 0.78, 95%CI 0.74-0.83, $p < 0.001$). Results in the ELSA-Brasil cohort, were similar: with a

higher mortality risk (HR 1.75, 95%CI 1.35-2.27; p<0.001) for those with estimated ECG-age of more than 8 years greater than the chronological age; and a lower mortality rate (HR 0.74, 95%CI 0.63-0.88; p<0.001) for those with ECG-age more than 8 years years less than the chronological age. In the SaMi-Trop cohort, patients with an ECG-age more than 8 years greater than the chronological age had a higher mortality risk (HR 2.42, 95%CI 1.53-3.83; p<0.001); for ECG-age more than 8 years smaller than the chronological age, however, the observed decrease in mortality risk was not statistically significant (HR 0.89, 95%CI 0.52-1.54; p=0.68)). Additional analysis also show that Cox model adjusted by sex and age presents a good performance in the prediction of 1-year mortality, with an area under the curve, AUC, of 0.80 (95%CI 0.79-0.81) for the CODE-15% cohort, 0.77 (95%CI 0.66-0.87) for the ELSA-Brasil and 0.74 (95%CI 0.68-0.80) for the SaMi-Trop.

The importance of the ECG-age in predicting mortality remains also when we adjust the model for cardiovascular risk factors. Hazard ratios for models adjusted by different selections of variables cardiovascular risk factors are given in Table 2. In this analysis, we additionally adjusted the model for hypertension, diabetes mellitus, and smoking habits, but this did not yield significant differences in the results. As in the first case, all associations (except for ECG-age more than 8 years smaller than the chronological age in the Sami-Trop cohort) remained significant with little change in the adjusted HR. We also did additional adjustments for dyslipidemia (CODE-15% and ELSA-Brasil cohorts) and obesity (ELSA-Brasil), without changing significantly the magnitude of the observed association.

Supplementary Table 1 presents baseline characteristics for each of the cohorts by ECG-age groups. We find that in all three cohorts, the group of patients with an ECG-age of more than 8 years greater than the chronological age have the lowest average chronological age (CODE-15%: 42.2; ELSA-Brasil: 48.5; SaMi-Trop: 54, p < 0.001 for t-

tests comparing average ages with the other ECG-age strata). Although seemingly contradictory, this is in accordance with the hypothesis that ECG-age is indeed a predictor of mortality. Since patients that have an ECG-age higher than their chronological age are more likely to die, older patients whose ECG-age is higher than their chronological age are not likely to be a part of the sample we are analyzing.

Electrocardiographic-age as a mortality predictor in apparently normal ECGs

Table 3 describes conventional ECG measurements for the participants in the three groups described above - i.e., a) patients with predicted ECG-age more than 8 years greater than their chronological age; b) more than 8 years smaller than their chronological age; and, c) within a range of 8 years from their chronological age. Although in the CODE-15% cohort statistically significant differences can be seen for all measurements ($p<0.001$ for all), these numbers do not yield a clinically significant difference. From a clinical perspective, these measurements can be considered remarkably similar to each other. In the ELSA-Brasil cohort, measurements were also numerically similar with a statistically significant difference obtained only for heart rate ($p<0.001$) and QTc interval ($p<0.001$).

To further evaluate whether the predicted ECG-age by the DNN was related to traditional electrocardiographic abnormalities, we performed an additional analysis, now restricted to normal ECGs from the CODE-15% and ELSA-Brasil cohorts. Which have, respectively, 80679 and 7691 participants with normal ECGs. We did not perform this analysis in the SaMi-Trop because most patients had ECG abnormalities related to Chagas disease. What was considered as normal ECG is defined in Methods. An analysis with a Cox model restricted to the normal ECG was performed and the obtained hazard ratios are displayed in Table 4. The same parameters of the analysis in Table 2 are used.

In the model adjusted by age and sex, ECG-age more than 8 years greater than the chronological age remained a statistically significant predictor of death risk in both cohorts (HR 1.53, 95% CI 1.30 – 1.80, p<0.001 in CODE-15% and HR 1.63, 95% CI 1.00 – 2.66 p=0.050 in ELSA-Brasil). On the other hand, ECG-age more than 8 years smaller than the chronological age remained associated with reduced risk of mortality in the CODE-15% (HR 0.66, 95% CI 0.57 - 0.76 p<0.001) but was not statistically significant in the ELSA-Brasil cohort (HR 0.91, 95% CI 0.68 - 1.21 p=0.502).

The results for models additionally adjusted for cardiovascular risk factors is also displayed in Table 4. After the adjustment, ECG-age more than 8 years greater than the chronological age was associated with increased risk of mortality in CODE-15% cohort (HR 1.52, 95% CI 1.29 - 1.79, p=0.015), but not in ELSA-Brasil (HR 1.49, 95% CI 0.91-2.43, p=0.114). This was also true for an ECG-age more than 8 years smaller than the chronological age. Risk was significantly decreased in CODE-15% cohort (HR 0.66, 95% CI 0.57 – 0.76, p<0.001) but not in ELSA-Brasil (HR 1.00, 95% CI 0.75 – 1.33, p=0.990). Which might be justified by the lack of statistical power due to the small number of deaths in this group for the ELSA-Brasil cohort (n=19). Additional adjustments for dyslipidemia (CODE-15% and ELSA-Brasil cohorts) and obesity (ELSA-Brasil) do not qualitatively change the results.

Electrocardiographic-age and cardiovascular risk factors

Figure 3(A) represents which cardiovascular risk factors were most likely associated with a predicted ECG-age more than 8 years greater than the chronological age considering all ECGs from ELSA-Brasil cohort. After logistic regression adjusted for age and sex, hypertension, diabetes, smoking and obesity remained significantly associated with an increased odds of having an ECG-age more than 8 years greater than the

chronological age. In Figure 3(B) the same model was applied only to participants with a normal ECG. Hypertension, diabetes and smoking were significantly associated with a predicted ECG-age more than 8 years greater than the chronological age.

Interpretability and time and frequency domain saliency maps

To assess whether ECG-age captures signals that can be interpreted by cardiologists, we conducted an additional experiment. We paired ECG-ages of subjects with the same chronological age, but where one of them had an ECG-age more than 8 years greater than their chronological age and the other more than 8 years smaller than their chronological age. Then, three medical doctors were asked to independently determine, for each pair, which ECG tracing was associated with the subject with higher ECG-age. Analyzing doctor's assessments of 134 pairs of traces, aggregated through majority voting, we found that they were not significantly better than random (chi square=3.0, p =0.12). We provide detailed results in Supplementary Table 2. Throughout the experiment, doctors were given feedback about their predictions (in Stage 2), this did not increase their accuracy in the subsequent stage. In fact, they performed worse in Stage 3 (Accuracy=45.5%), after the feedback, than in Stage 1 (Accuracy=64.4%), before the feedback, or in Stage 2 (Accuracy=62.2%), during the feedback.

Additionally, we randomly generated 50 pairs of normal ECG tracings, with saliency maps[21] highlighting the regions in the ECG tracing that have the highest impact in the predicted ECG-age (see Methods). Supplementary Fig 1 provides some illustrative examples. We asked the same set of three medical doctors to qualitatively analyze which sections of the ECG were being frequently highlighted by the visualization algorithm. Doctors independently suggested that low-frequency components, as P and T waves, were disproportionately highlighted.

We also generate saliency maps in the frequency domain giving the relative importance of each frequency component for the final prediction (see Methods). Supplementary Fig 2 shows the median and interquartile range from this analysis for 100 normal exams in each cohort. The analysis suggests the frequency component between 8 and 15 Hz of the ECG spectrum are the ones that most contribute to the model prediction.

A fine-grained analysis of the relation between ECG-age and mortality

In most of the discussion in this paper we use a hard threshold of 8 years old between the predicted ECG-age and the chronological age to separate the patients into different risk groups. In Supplementary Fig 4, we present an alternative setup where we split the patients into 5 quintiles of the difference of predicted ECG-age and chronological age and show adjusted survival, hazard ratios and 95% confidence intervals for these groups. The results indicate that the groups where predicted ECG-age is lower than the chronological age (Q1 and Q2) had a lower risk of mortality and the groups Q4 and Q5 had a higher risk of mortality. Both when all exams are considered and when only normal exams are considered.

TABLES AND FIGURES

Table 1: Baseline characteristics. The table summarizes the characteristics of the three cohorts analysed in this study. It includes the baseline characteristics, the summary of follow-up time, and the number of events.

	CODE-15% (n = 218169)	ELSA-Brasil[b] (n = 14263)	SaMi-Trop[c] (n=1631)
Characteristics[a]			
Sex, male, n (%)	88508 (41)	6494 (46)	550 (34)
Age (years), mean (s.d.)	51 (20)	52 (9)	60 (13)
Hypertension, n (%)	64767 (30)	5108 (36)	593 (36)
Diabetes, n (%)	13720 (6)	2830 (20)	161 (10)
Smoking, n (%)	13645 (6)	1882 (13)	498 (31)
Previous myocardial infarction, n (%)	1553 (0.7)	258 (1.8)	76 (5)
Follow-up(years), median (IQR)	3.4 (2.1-5.0)	9.8 (8.9-10.0)	2.1 (2.0-2.2)
Events, n (%)	8110 (3.7)	617 (4.3)	104 (6.4)

[a] Data are expressed as number (percentage) unless otherwise indicated

[b] There are missing values in variables from the ELSA-Brasil cohort (Hypertension, 13; Diabetes, 3; Smoking, 1; Previous myocardial infarction, 7); valid percentages are reported

[c] There are missing values in a variable from the SaMi-Trop cohort (Smoking, 6); valid percentages are reported

Figure 1: Chronological *vs* ECG-age. The scatter plots display the relation between the predicted ECG-age and chronological age. The black line is the identity line. The lateral histograms show the distributions of predicted ECG-age and chronological age among patients of the cohorts. (a) CODE-15% cohort, (b) ELSA-Brasil cohort, (c) SaMi-Trop cohort. The mean predicted ECG-age was 52 (s.d. 19), 47 (s.d. 11), 63 (s.d. 14), for CODE-15%, ELSA-Brasil cohort and SaMi-Trop cohort, respectively. The R squared (Pearson correlation) was 0.71 (r = 0.84) in the CODE-15%, 0.32 (r=0.57) in ELSA-Brasil cohort and 0.35 (r=0.59) in the SaMi-Trop cohort.

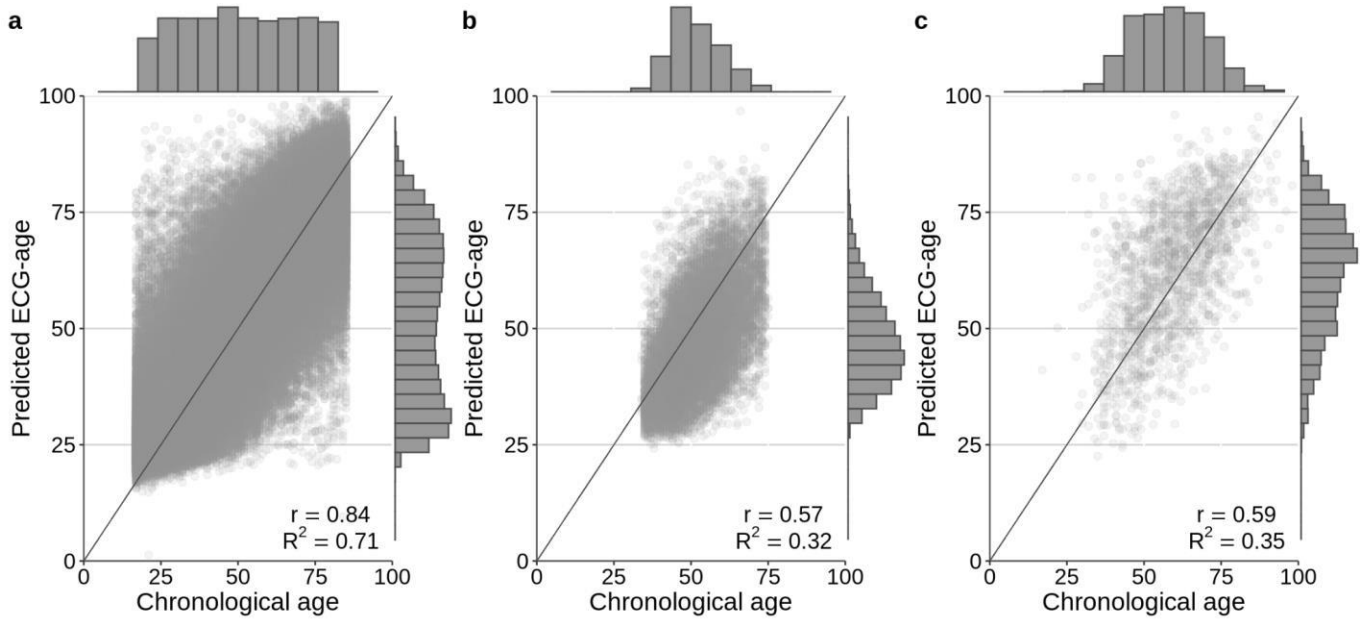


Table 2: Risk of death. The table displays the hazard ratios (HR) when the difference between ECG-age and chronological age are larger than 8 years (either positive or negative). The HR summarizes the Cox regression models obtained for overall mortality. The models were adjusted by different selection of variables (including age, sex and cardiovascular risk factors).

	CODE-15% (n = 218169)			ELSA-Brasil (n = 14263)			SaMi-Trop (n=1631)	
	HR (CI 95%)		p	HR (CI 95%)		p	HR (CI 95%)	p
Adjusted by **age and sex**								
ECG-age < age-8y	0.78	(0.74-0.83)	<0.001	0.74	(0.63-0.88)	<0.001	0.89 (0.52- 1.54)	0.681
ECG-age > age+8y	1.79	(1.69-1.90)	<0.001	1.75	(1.35-2.27)	<0.001	2.42 (1.53- 3.83)	<0.001
Adjusted by age, sex, **hypertension, diabetes mellitus and smoking**								
ECG-age < age-8y	0.78	(0.74-0.83)	<0.001	0.82	(0.69-0.98)	0.030	0.90 (0.52- 1.55)	0.702
ECG-age > age+8y	1.79	(1.68-1.89)	<0.001	1.56	(1.20-2.03)	<0.001	2.48 (1.56- 3.94)	<0.001
Adjusted by age, sex, hypertension, diabetes mellitus, smoking **and dyslipidemy**								
ECG-age < age-	0.78	(0.74-	<0.00	0.82	(0.69-	0.030	Not available	

8y	0.83)	1	0.98)			
ECG-age > age+8y	1.78 (1.68-1.89)	<0.001	1.56 (1.20-2.03)		<0.001	
Adjusted by age, sex, hypertension, diabetes mellitus, smoking, dyslipidemy **and obesity**						
ECG-age < age-8y	Not available		0.82 (0.69-0.98)		0.030	Not available
ECG-age > age+8y			1.57 (1.21-2.04)		<0.001	

The number of death events was n=8118 for CODE-15%, n=617 for ELSA-Brasil and n=104 for SaMi-Trop. When the ECG-age is more than 8 years smaller than the chronological age n=1861, n=239 and n=19, respectively, for the CODE-15%, ELSA-Brasil and SaMi-Trop cohorts. When the ECG-age is more than 8 years greater than the chronological age n=1675, n=69 and n=41, respectively.

Figure 2: Adjusted survival curves. The plots display the survival curves for the different cohorts. (**a**) CODE-15% cohort, (**b**) ELSA-Brasil cohort, (**c**) SaMi-Trop cohort. The curves are computed from the age and sex-adjusted Cox proportional model for all-cause mortality. Three groups of patients are taken into consideration: those with ECG-age more than 8 years greater than the chronological age (denoted by: ">8 years older") ; those with ECG-age within a range of 8 years from their chronological age (denoted by: "± 8 years"); and, those with ECG-age more than 8 years smaller than the chronological age (denoted by: ">8 years younger").

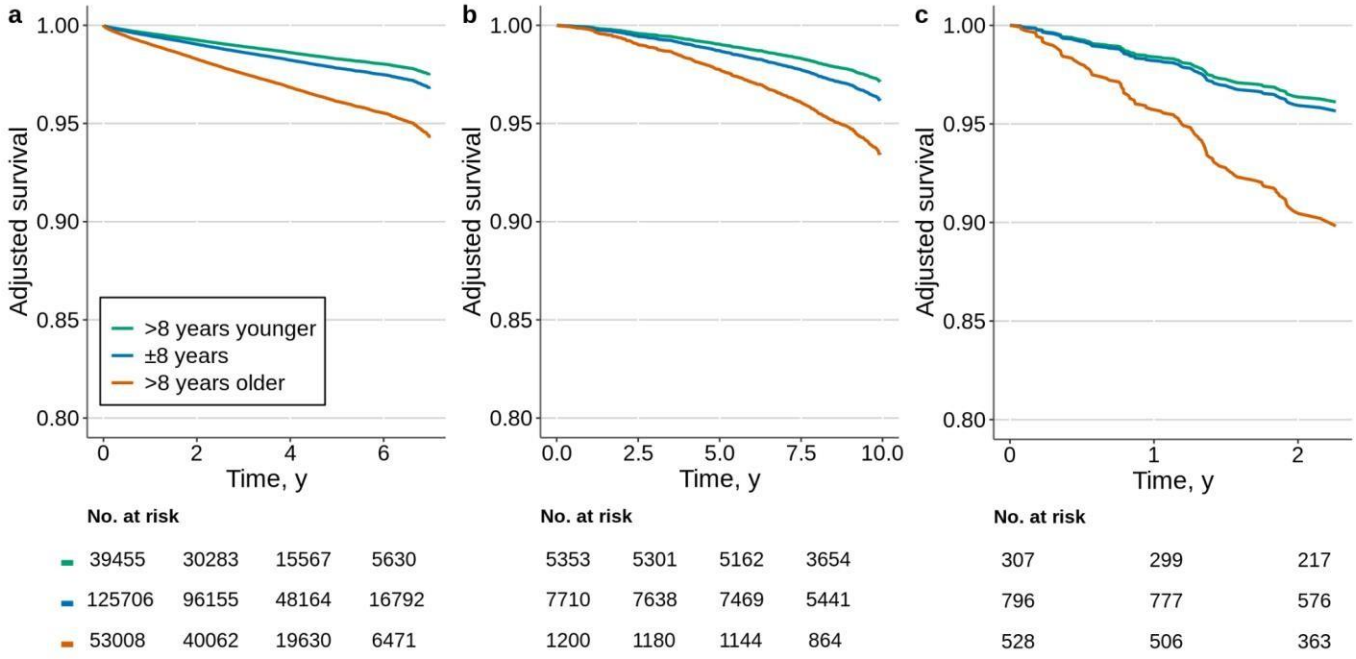


Table 3: ECG measurements. The table displays the median, and ("under parentesis") the interquartile range, for the ECG measurements. It considers three groups of patients: those with ECG-age more than 8 years greater than the chronological age (denoted by: ">8 years older") ; those with ECG-age within a range of 8 years from their chronological age (denoted by: "± 8 years"); and, those with ECG-age more than 8 years smaller than the chronological age (denoted by: ">8 years younger"). Statistical comparison of the medians is made through Kruskal-Wallis two-sided test.

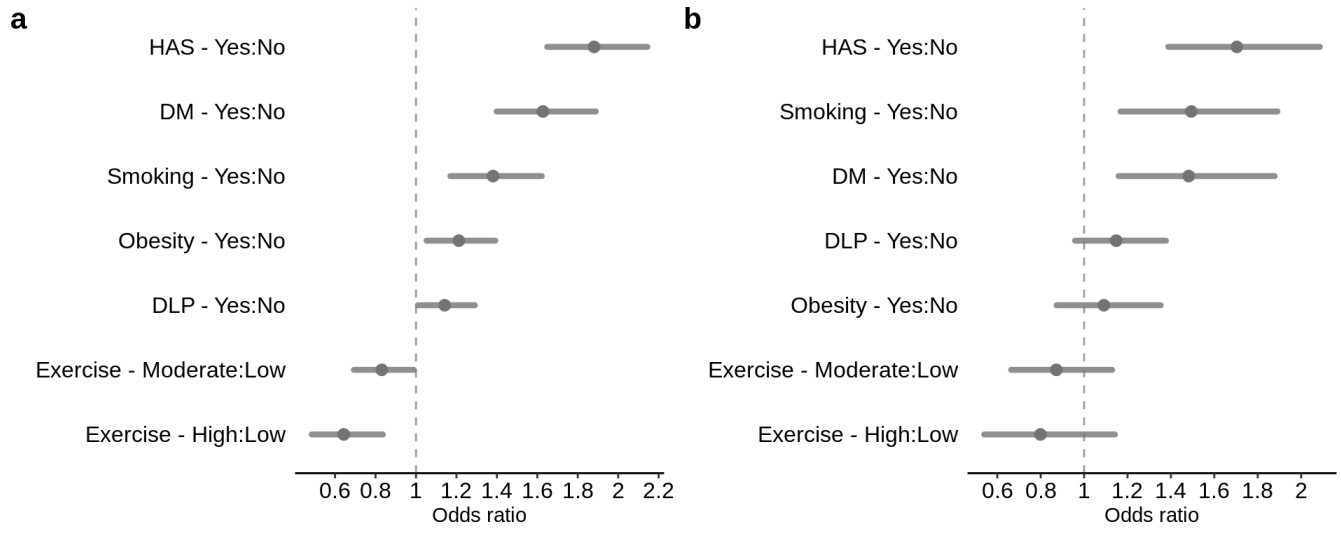
	CODE-15% (n=80679)				ELSA-Brasil (n=7691)			
	± 8 years	>8 years younger	>8 years older	p	± 8 years	>8 years younger	>8 years older	p
Heart rate (bpm)	70 (63-78)	70 (62-79)	71 (64-79)	<0.001	66 (61-72)	64 (59-71)	69 (63-75)	<0.001
P duration (ms)	106 (100-114)	108 (100-116)	108 (100-116)	<0.001	108 (102-116)	110 (102-116)	108 (100-116)	0.558
QRS axis	47 (27-65)	45 (25-62)	43 (24-60)	<0.001	44 (21-60)	43 (20-61)	44 (19-61)	0.737
QRS duration (ms)	90 (84-96)	90 (84-96)	92 (84-98)	<0.001	86 (80-92)	86 (82-92)	86 (80-90)	0.068
Average RR interval (ms)	845 (757-942)	845 (750-950)	837 (750-932)	<0.001	-	-	-	-
QTc (ms)	411 (400-424)	413 (401-425)	413 (401-425)	<0.001	416 (405-427)	414 (403-426)	418 (406-429)	<0.001

Table 4: Hazard Ratios for normal ECGs. The table displays, for patients with a normal ECG, the hazard ratios (HR) according to the differences between ECG-age and chronological age. The HR summarizes the Cox regression models obtained for overall mortality. The models were adjusted by different selection of variables (including age, sex and cardiovascular risk factors).

	CODE-15% (n=80679)		ELSA-Brasil (n=7691)	
	HR (CI 95%)	P	HR (CI 95%)	p
Adjusted by **age and sex**				
ECG-age < age-8y	0.66 (0.57 – 0.76)	<0.001	0.91 (0.68 – 1.21)	0.502
ECG-age > age+8y	1.53 (1.30 – 1.80)	<0.001	1.63 (1.00 – 2.66)	0.050
Adjusted by age, sex, **hypertension, diabetes mellitus and smoking**				
ECG-age < age-8y	0.66 (0.57 – 0.76)	<0.001	1.00 (0.75 – 1.33)	0.990
ECG-age > age+8y	1.52 (1.29 - 1.79)	<0.001	1.49 (0.91 – 2.43)	0.114
Adjusted by age, sex, hypertension, diabetes mellitus, smoking **and dyslipidemy**				
ECG-age < age-8y	0.66 (0.57 – 0.76)	<0.001	1.00 (0.75 – 1.33)	0.990
ECG-age > age+8y	1.52 (1.29 - 1.79)	<0.001	1.49 (0.91 – 2.43)	0.114
Adjusted by age, sex, hypertension, diabetes mellitus, smoking, dyslipidemy **and obesity**				
ECG-age < age-8y	Not available		1.00 (0.75 – 1.33)	0.992
ECG-age > age+8y			1.42 (0.86 – 2.35)	0.171

The number of events was n = 1074 for CODE-15% and n = 228 for ELSA-Brasil. The number of events when ECG-age is more than 8 years smaller than the chronological age there were, n=249 and n=105 for CODE-15% and ELSA-Brasil, respectively. Considering ECG-age is more than 8 years greater than the chronological age there were n=203 and n=19 events for CODE-15% and ELSA-Brasil, respectively.

Figure 3: Adjusted odds ratios (ORs) for the ELSA-Brasil cohort. The figure shows the adjusted ORs of the ECG-age being more than 8 years greater than the chronological age for risk factors. (**a**) All patients; and, (**b**) only for patients with normal ECG. The dots represent the adjusted ORs (by age and sex) and the horizontal lines represent the corresponding 95% CIs.



Supplementary Table 1: Baseline characteristics by ECG-age groups. Display baseline characteristics for three groups of patients: those with ECG-age more than 8 years greater than the chronological age (denoted by: ">8 years older") ; those with ECG-age within a range of 8 years from their chronological age (denoted by: "± 8 years"); and, those with ECG-age more than 8 years smaller than the chronological age (denoted by: ">8 years younger").

	CODE-15%			ELSA-Brasil			SaMi-Trop		
Characteristics	± 8 years (n=125706)	>8 years younger (n=39455)	>8 years older (n=53008)	± 8 years (n=7710)	>8 years younger (n=5353)	>8 years older (n=1200)	± 8 years (n=796)	>8 years younger (n=307)	>8 years older (n=528)
Sex, Male, n (%)	50821 (40)	15508 (39)	22179 (42)	3403 (44)	2536 (47)	555 (46)	259 (33)	102 (33)	189 (36)
Age, years, mean (s.d.)	50.5 (20)	63.0 (15)	42.2 (17)	49.0 (12)	55.0 (13)	48.5 (12)	62.0 (20)	64.0 (19)	54.0 (16)
Hypertension, n (%)	36418 (29)	15604 (40)	12745 (24)	2695 (35)	1902 (36)	511 (43)	288 (36)	120 (39)	185 (35)
Diabetes, n (%)	7808 (6)	3462 (9)	2450 (5)	1439 (19)	1121 (21)	280 (23)	81 (10)	38 (12)	42 (8)
Smoking, n (%)	7595 (6)	2522 (6)	3528 (7)	1065 (14)	610 (11)	207 (17)	239 (30)	92 (30)	167 (32)
Previous myocardial infarction, n (%)	885 (0.7)	358 (0.9)	310 (0.6)	132 (1.7)	95 (1.8)	31 (2.6)	40 (5.0)	7 (2.3)	29 (5.5)

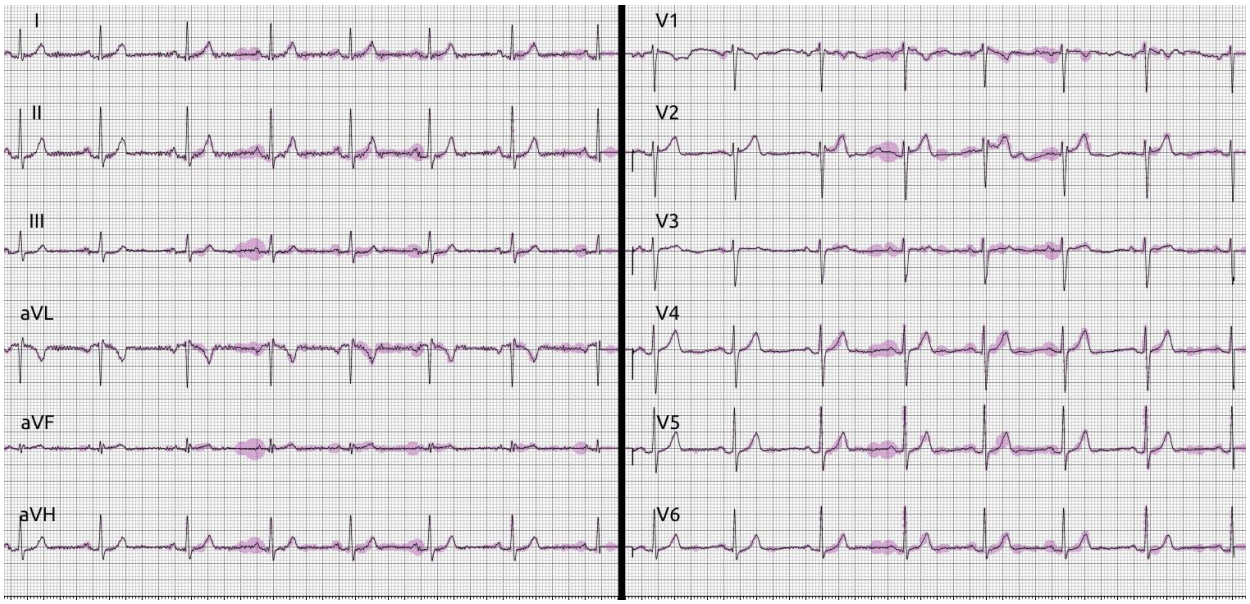
Data are expressed as numbers (percentage) unless otherwise indicated

Supplementary Table 2: Medical doctors discerning the ECG-age. The table displays the results for the ECG reading experiment. Medical doctors annotated 134 ECGs in three rounds. Given two options A and B, they had to decide which one had an ECG-age more than 8 years greater than their chronological age. Doctors were given the chronological age of the two patients (which were the same), and two traces. In Stage 2, doctors were given the answer after accomplishing the task (i.e., whether their assessment was correct), this yielded no difference in Stage 3. Overall, these results suggest that ECG-age captures signals that are non-trivial for doctors to distinguish.

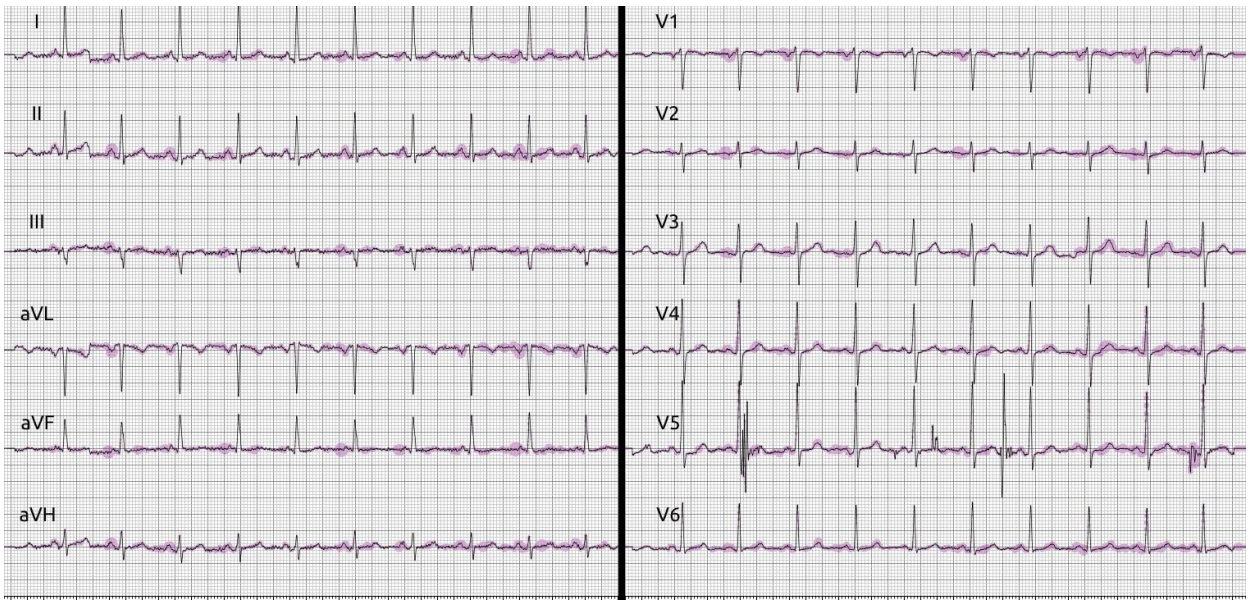
		Stage 1 n=45 Acc=64.4%		Stage 2 n=45 Acc=62.2%		Stage 3 n=44 Acc=45.5%		Aggregated n=134	
		Correct Answer							
Given Answer		A	B	A	B	A	B	A	B
	A	19	9	12	6	8	10	41	26
	B	7	10	11	16	14	12	30	37
		chisq=2.1, p=0.15		chisq=1.96 p=0.16		chisq=0.94 p=0.76		chisq=3.0, p=0.08	

Supplementary Figure 1: Saliency maps. Illustrative example of ECGs with saliency maps. Saliency maps are displayed overlayed with the ECG signal. The size of the blue dots superimposed with the ECG trace is proportional to the partial derivative of the ECG-age prediction regarding that point of the input tracing.

A)

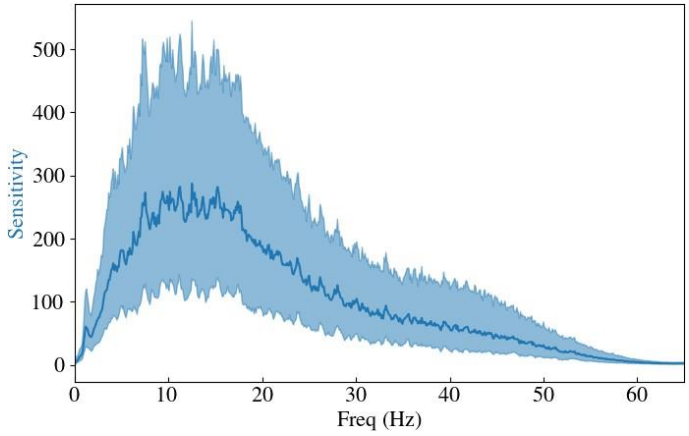


B)

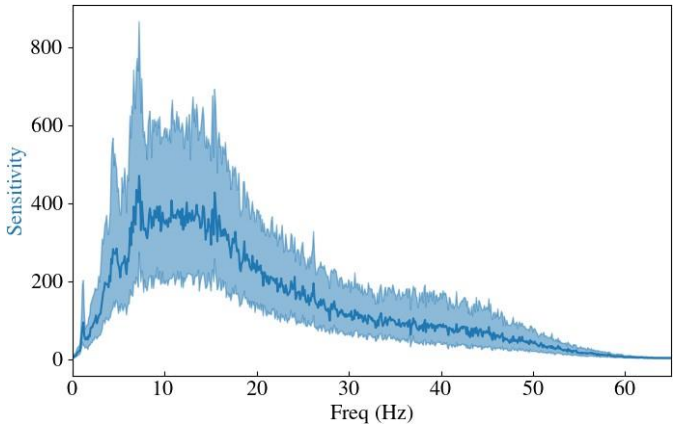


Supplementary Figure 2: Saliency maps in the frequency domain. We analyze the local sensitivity in the frequency domain and show the relative importance of each frequency component in the DNN prediction (see Methods for a precise interpretation). The analysis is performed for 100 normal ECGs randomly sampled from CODE-15%, ELSA-Brasil, and Sami-Trop with similar results. The full line is the median and the shaded region gives the interquartile range over the 100 evaluated samples.

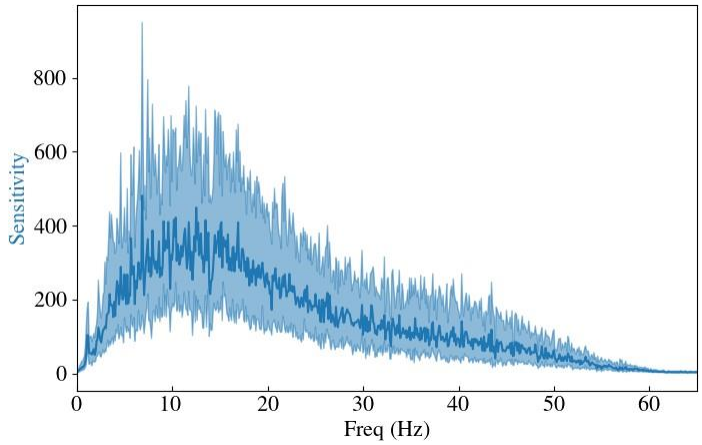
A) CODE-15%



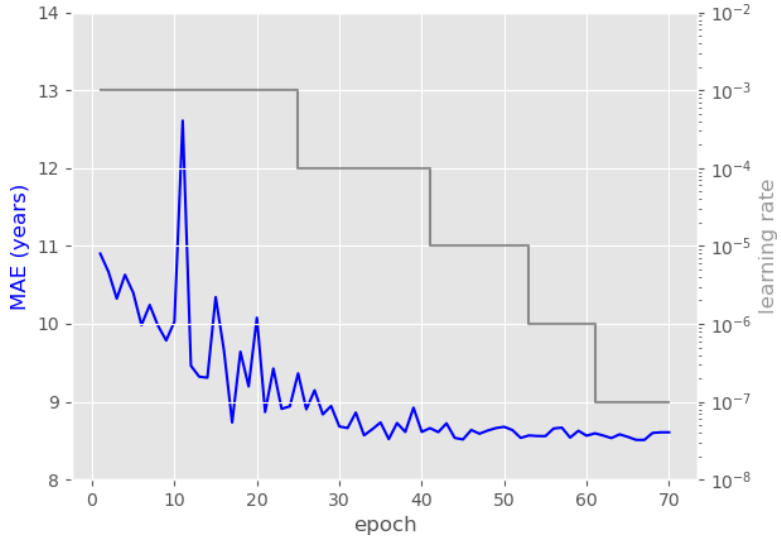
B) ELSA-Brasil



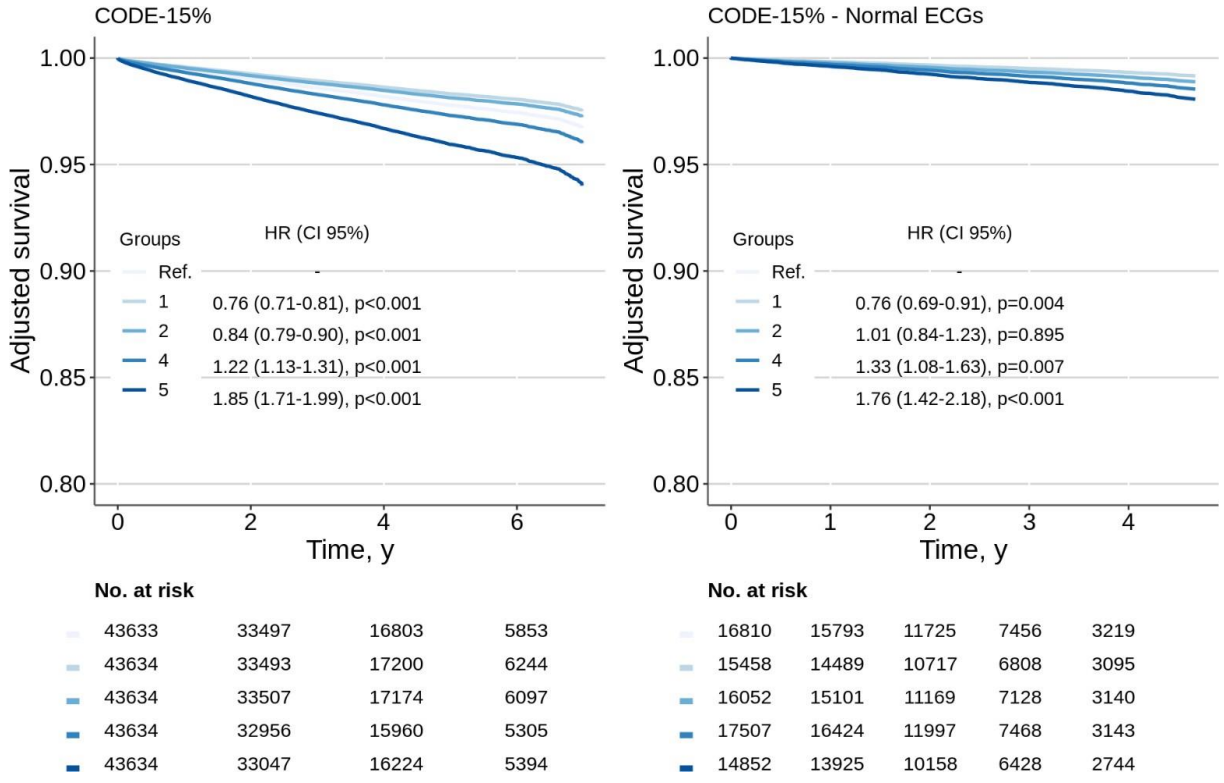
C) Sami-Trop



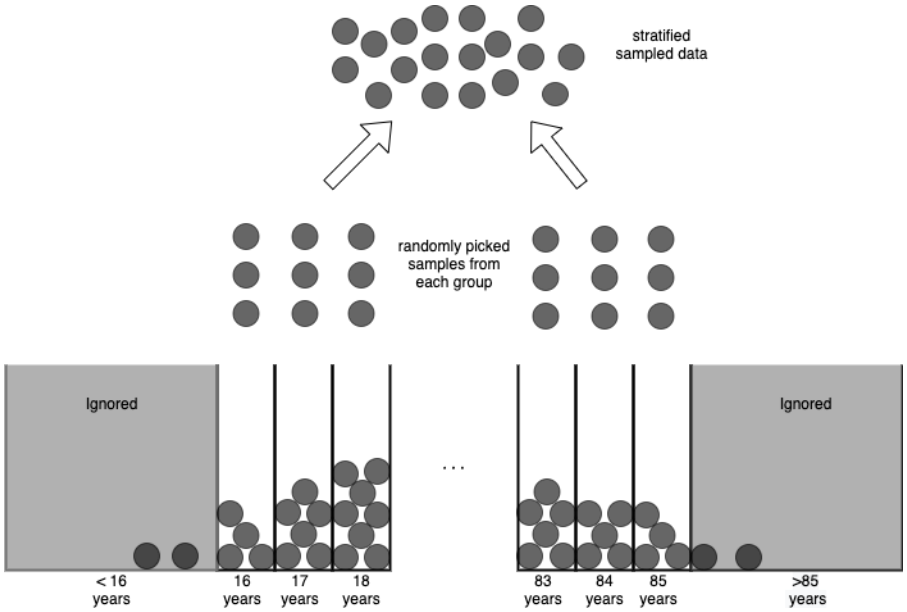
Supplementary Figure 3: Learning curve. In blue, the plot displays the mean absolute error (MAE) computed in the 5% validation set. In gray, it shows the learning rate used. The x-axis gives the epochs: each epoch a full pass through the set of training examples updating the model weights. The best model is obtained in epoch 66 with MAE=8.5097 on the validation set.



Supplementary Fig 4. Adjusted survival curve for patients‘ quintiles. Adjusted survival curves, hazard ratios (HR) and CIs 95% for 5 groups of the difference between ECG-age and chronological age. The patients were divided into quintiles according to quintiles of the difference of ECG-age and chronological age. The HR summarizes the Cox regression models obtained for overall mortality. The models were adjusted by age and sex.



Supplementary Fig 5: Illustrative representation of stratified sampling. We illustrate the stratified sampling used to generate the CODE-15% dataset. Each ECG exam is represented by a disk. The exams are divided into age groups with one group for each age, ranging from 16 to 85 years old. The same number of samples from each age group is then randomly picked to be assigned to the CODE-15% dataset. The same procedure is used to generate the 5% split used for validating the model.



Discussion

In this paper, we use a data-driven approach to obtain a model that predicts age from the raw ECG tracing. By having the chronological age of the person as the prediction target, we expect the trained model to learn to capture, on average, how aging affects the ECG exam. Indeed, having a predicted ECG-age higher than one's actual age is an indication that the exam is similar to those of older people, who have a higher associated cardiovascular risk and are more likely to die from cardiovascular diseases. We show that classical cardiovascular risk factors are associated with having an ECG-age more than 8 years greater than the chronological age. For some risk factors, such as hypertension, diabetes mellitus, and smoking, the association remains even when only normal ECGs

were considered (cf. Figure 3). Moreover, this study shows, in three different cohorts, that the difference between the ECG-age and the chronological age can be used as a marker of the risk of death.

From a clinical perspective, ECG-age may present itself partly as a natural summary index of ECG changes and abnormalities accumulated during the life course of each subject. ECG tracings are affected by a large number of factors and mechanisms and, while summarizing them in a single number is a huge oversimplification, it can still be useful. It transmits the idea of cardiovascular risk in a language that does not require medical expertise and can be understood by patients and other professionals without medical training. In the literature, an AI-based model that predicts the probability of 1-year mortality have been recently proposed[8] and could also play a similar role. Nonetheless, reporting the ECG-age seems more intuitive from a patient perspective and, probably, easier to be used in clinical practice.

The analyses suggest that ECG-age is capable of capturing more than traditional ECG abnormalities or underlying conditions. Over-estimation of ECG-age was significantly associated with death after controlling for age and sex, cardiovascular risk factors and, even, when calculated only for subjects with normal ECGs. In the case of normal ECGs, this association was significant in CODE-15% but not in the ELSA-Brasil cohort. This might be explained by the small number of deaths in the ELSA-Brasil cohort or by the poorer annotation of risk factors in the CODE-15% study, in which this information is self-reported and obtained during the clinical activity. Moreover, ECG measurements were also not meaningfully different in the groups with predicted ECG-age more than 8 years greater than, more than 8 years smaller than, and within a range of 8 years from their chronological age.

Since the maintenance of a normal ECG status over time is associated with a low risk of cardiovascular diseases in a dose-response relationship[22], we hypothesize that the DNN might be able to identify subtle abnormalities that are not being currently identified in traditional analysis. This could help justify the capacity of evaluating the risk even for apparently normal ECGs. The lack of capability of trained doctors to distinguish between pairs of normal ECGs of the same age but different ECG-age (see **Supplementary Table 2**) also supports this hypothesis.

The advance of interpretable machine learning algorithms[23] might make it possible to leverage the features used by these models into clinical practice. Our initial insights on the mechanisms used for the estimation of ECG-age - and its prognostic value - suggest that low-frequency components of the ECG, usually associated with P and T waves, might play an important role although these considerations would deserve a specific and more detailed investigation.

Despite being part of the routine evaluation of many patients in both primary and specialized care, the role of ECG exams are low-cost and widely available, the role in cardiovascular disease prediction and, hence, prevention is not as clear. Its prognostic impact has been explored in previous publications [24,25], nonetheless, the available methods are not widely adopted as a screening tool for individuals free of cardiovascular disease[26]. Our study is a further step towards a more practical use of the ECG in prognostic evaluation, considering that ECG-age can be a marker of the biological age of the cardiovascular system, or "cardiovascular age". This concept was introduced in previous studies[27,28] with the purpose of improving risk communication and patient adherence to proposed interventions. There, however, the value does not provide additional information to what the calculated risk already informs (since it is calculated based only on them). Doctors often struggle in decision making regarding treatment for

primary prevention of cardiovascular diseases in intermediate risk patients. Identifying new risk modifiers that can potentially improve risk prediction in this population (either by a positive net reclassification index or by derivation of a new predictive model) is paramount. This is specially true if such a marker is derived from an inexpensive and widely available tool such as the ECG. The analysis presented here shows that the ECG-age can inform on risk that is not accounted for in traditional cardiovascular risk factors. And, in this sense, the concept can go beyond the concept of "cardiovascular age" proposed in previous studies [27,28].

Our work is perhaps best understood in the context of its limitations. The use of end-to-end DNN models is central to this work and yielded interesting findings (such as the possibility of predicting mortality even for apparent normal ECGs). Nonetheless, the complexity of these models makes it hard to fully interpret the results. Our exploratory analysis included sensitivity analysis both in the time and frequency domain and the analysis and review of more than one hundred ECGs by trained cardiologists. While it did provide some insight on what is being detected by the model, it is far from sufficient to completely explain the findings. Furthermore, while our study demonstrates the potential clinical utility of the ECG-age in individual risk prediction, further studies are desired to evaluate its incorporation in the clinical practise, including its use in addition to established risk calculators for primary prevention of cardiovascular diseases.

Here, we present the mortality risk prediction as a downstream task. That is, a model that was trained for predicting the patient's age is later used for a different task: that of mortality prediction. This shows the model is useful in scenarios that it has not been explicitly trained on and when used in a simple linear cox model it can help separate patients in different risk groups. Nonetheless, one possible limitation of this analysis is that the relations considered in this second step are only the linear ones. Hence, taking into

consideration nonlinear relations in this second step could possibly modify the observed relationship.

To conclude, the predicted ECG-age may reflect biological age and it is a promising tool for risk prediction of overall mortality. It summarizes the information from the ECG in a single index with a clear interpretation for the patient. Data for training these models are also easy to obtain: while producing large datasets fully annotated with electrocardiographic abnormalities requires many hours of work by trained physicians, self-reported age is usually easy information to come by. Finally, the ability to predict mortality even for normal ECGs suggests that there might still be subtle electrocardiographic markers and abnormalities that are of interest and are not being captured in traditional analysis and the models presented here might be a useful tool in trying to find them.

Methods

Ethics declarations

This study complies with all relevant ethical regulations. CODE Study was approved by the Research Ethics Committee of the Universidade Federal de Minas Gerais, protocol 49368496317.7.0000.5149. Since this is a secondary analysis of anonymized data stored in the TNMG, informed consent was not required by the Research Ethics Committee for the present study. ELSA-Brasil was approved by the Research Ethics Committees of the participating institutions and by the National Committee for Research Ethics (CONEP 976/2006) of the Ministry of Health. Sami-Trop study was approved by the Brazilian National Institutional Review Board (CONEP), No. 179.685/2012. In both investigations, all human subjects were adults who gave written informed consent. All researchers who deal with datasets signed terms of confidentiality and data utilization.

The CODE cohort

Clinical Outcomes in Digital Electrocardiography (CODE) study[17] was developed with the database of digital ECG exams of the TeleHealth Network of Minas Gerais (TNMG)[29,30], Brazil, linked to the public databases of the Mortality and Hospitalization Information Systems. It was expected that the consolidated database would be useful for multiple purposes, including the evaluation of the epidemiological and prognostic significance of ECG findings[31] and the development of new methods of automatic classification of ECG abnormalities[3], using both conventional statistical methods and new machine learning techniques.

Patients over 16 years old with a valid ECG performed from 2010 to 2017 were included. Clinical data were self-reported. A hierarchical free-text machine learning algorithm recognized specific ECG diagnoses from cardiologist reports. The Glasgow ECG Analysis Program provided Minnesota Codes and automatic diagnostic statements. For the CODE database, the presence of a specific electrocardiographic diagnosis was considered automatically when there was an agreement between the diagnosis extracted from the cardiologist report and the automatic report from Glasgow Diagnostic Statements or Minnesota code. In cases where there were discordances between medical reports and one of the automatic programs, a manual revision was done by trained cardiologists[17].

The electronic cohort was obtained linking data from the ECG exams (name, sex, date of birth, city of residence) and those from the national mortality information system, using standard probabilistic linkage methods (FRIL: Fine-grained record linkage software, v.2.1.5, Atlanta, GA). After the linkage, the data was anonymized for storage[17].

From a dataset of 2,470,424 ECGs, 1,773,689 patients were identified. After excluding the ECGs with technical problems and patients under 16 years old, a total of 1,558,415 patients were included for analyses. The mean age was 51.6 [s.d.17.6] years with 40.2% male. The overall mortality rate was 3.34% in a mean follow-up of 3.7 years[17].

The model was also evaluated in two established cohorts, the São Paulo-Minas Gerais Tropical Medicine Research Center (SaMi-Trop)[19] of Chagas disease patients and the Longitudinal Study of Adult Health (ELSA-Brasil)[18], of Brazilian public servants, in which raw ECG tracings from the baseline and follow-up with total mortality as the end-point are available. These cohorts are described next.

The CODE-15% cohort

The CODE-15% is a subset of the CODE cohort. The CODE cohort was divided into 85-15% splits, with the 85% split being used for developing the model and 15% hold-out being the one used in subsequent analyses and referred to as CODE-15%. This hold-out set is obtained by a stratified sampling procedure, where the stratification is made with respect to the patients age. The procedure is illustrated in Supplementary Fig 5. Given all the exams from the original CODE cohort, we group the exams by the age of the patient at the time of the examination. One group for each age ranging from 16 to 85 years, i.e. a total of 70 uniformly spaced age groups. The CODE-15% cohort is obtained by picking the same number of exams (~3100) at random from each age group. The result is an, approximately, uniform age distribution from 16 years to 85 years. Only the first patient exam is considered in all the analysis with this cohort and the remaining exams from the patients are removed from the remaining data and not used in the analysis. We do not sample from patients older than 85 or younger than 16 years, which do not appear in the CODE-15% cohort.

The ELSA-Brasil cohort

ELSA-Brasil is a cohort study that aims to investigate the development of chronic diseases, primarily diabetes and cardiovascular diseases, over a long-term follow-up.[32,33] All active or retired employees of the six institutions (and, in a few instances, also of related educational or health institutions) from six Brazilian capitals, of both sexes, and with ages between 35 and 74 years, were eligible for the study. Exclusion criteria were severe cognitive or communication impairment, intention to quit work at the institution in the near future for reasons not related to retirement, and, if retired, residence outside the corresponding metropolitan area. Women with current or recent pregnancy were

rescheduled so that the first interview could take place ≥4 months after delivery. A total of 15,105 participants were enrolled, 6887 men and 8218 women, thus giving reasonably large numbers for sex-specific analyses. Baseline assessment (2008-10) included detailed interviews and measurements to assess social and biological determinants of health, as well as various clinical and subclinical conditions related to diabetes, cardiovascular diseases, and mental health. A second and third visit of interviews and examinations were done (2012-14 and 2017-2019) to enrich the assessment of cohort exposures and to detect initial incident events. Annual surveillance has been conducted since 2009 for the ascertainment of incident events. Biological samples (sera, plasma, urine, and DNA) obtained at both visits have been placed in long-term storage. In a mean of 9.36 years of follow-up, 14,263 (94,5%) participants were followed, until 01/01/2020, 617 (4.3%) died and 842 (5.6%) were lost to follow-up.

The SaMi-Trop cohort

SaMi-Trop is an NIH-funded prospective cohort of 1959 patients with chronic Chagas cardiomyopathy to evaluate whether a clinical prediction rule based on ECG, brain natriuretic peptide (BNP) levels, and other biomarkers can be useful in clinical practice.[19,34] The study is being conducted in 21 municipalities of the northern part of Minas Gerais State in Brazil with at least 2 years of follow-up, including one visit at baseline and another at 24 months. Eligible patients were selected based on the ECG results performed in 2011-2012 by the Telehealth Network of Minas Gerais, which from now on will be called index ECG. Only patients who fulfilled all of the following inclusion criteria were selected:
(1) self-reported Chagas disease; (2) an index ECG reported as abnormal and (3) aged 19 years or more. The exclusion criteria included pregnancy or breastfeeding, and any life-threatening disease with an ominous prognosis that suggested a life expectancy of <2

years. The baseline evaluation included a collection of sociodemographic information, social determinants of health, health-related behaviors, comorbidities, medicines in use, history of previous treatment for Chagas disease, functional class, quality of life, blood sample collection, and ECG. Patients were mostly female, aged 50–74 years, with low family income and educational level, with known Chagas disease for >10 years; 46% presented with functional class >II. Previous use of benznidazole was reported by 25.2% and permanent use of pacemaker by 6.2%. Almost half of the patients presented with high blood cholesterol and hypertension and one-third of them had diabetes mellitus. N-terminal of the prohormone BNP (NT- ProBNP) level was >300 pg/mL in 30% of the sample. Clinical and laboratory markers predictive of severe and progressive Chagas disease were identified as high NT-ProBNP levels, as well as symptoms of advanced heart failure [34]. During a mean follow-up of 2.09 years, 1631 patients were being followed until the 2nd visit. 104 (6.4%) died and 328 (16.7%) were lost to follow-up.

Electrocardiographic and clinical definitions in CODE and ELSA-Brasil

An ECG was considered ¯normal‖ in the CODE cohort according to conventional clinical reporting and by having automatic measurements by the Glasgow software within the normal range. In the ELSA-Brasil and Sami-Trop cohorts, ECGs were codified by the Minnesota code[18,35] with manual review of a trained cardiologist. Those with no major or minor abnormalities according to the criteria were considered normal.

All clinical risk factors included in the CODE cohort were self-reported in a clinical standardized questionnaire. Hypertension, diabetes and dyslipidemia were also considered if informed use of antihypertensives, oral hypoglycemic agents or insulin, statins or fibrates; respectively. In the Sami-Trop cohort, the risk factors were also self-reported in a baseline interview. In the ELSA-Brasil study, hypertension was defined as

systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, or verified treatment with anti-hypertensive medication during the past 2 weeks; diabetes mellitus as a report of a previous diagnosis of diabetes, or the use of medication for diabetes, or meeting a diagnostic value for diabetes according to one of the following tests: fasting or 2-h plasma glucose obtained during a 75-g oral glucose tolerance test or HbA1C; dyslipidemia as either a total cholesterol ≥ 240mg/dl, LDL cholesterol ≥ 160 mg/dl, HDL cholesterol < 40 mg/dl or triglycerides ≥ 150 mg/dl; obesity as BMI ≥30 kg/m2 and smoking by participants self-report.

The model

Exams from patients in the CODE cohort that were not included in the hold-out set CODE-15% (see section above) were used to develop a convolutional DNN to predict age. This split contains 85% of the patients and was further divided into 80-5% splits: being the first used to learn the neural network weights, and the samples from the 5% remaining patients used for comparing design choices and adjusting optimization parameters.

The 5% validation split for is obtained by using a stratified sampling procedure. The procedure is illustrated in Supplementary Fig. 4 and is similar to the one used for generating the CODE-15% cohort. *G*iven all the patients that are not in the CODE-15% cohort, we group their exams by the age of the patient at the moment it was taken. One group for each age ranging from 16 to 85 years. The 5% validation set is then obtained by sampling the same number of exams (~1600) at random from each age group. As for the CODE-15% cohort, such a procedure aims to guarantee an, approximately, uniform age distribution in the validation set, by picking the same number of patient exams for equally-spaced one-year intervals. The training dataset is composed of all exams from the 80% remaining patients. The training dataset has an unbalanced distribution of ages and, to

correct for it during the training procedure, we weight the exam records inversely proportional to the frequency of patients with that given age.

The architecture and the set of hyperparameters are described next and are similar to a previous study[3], for which the DNN was trained to detect 6 types of ECG abnormalities (considered representative of both rhythmic and morphologic ECG abnormalities) on the same dataset. The results with this choice of hyperparameters were considered satisfactory and no further hyperparameter search was performed.

We used a convolutional neural network similar to the residual network proposed for image classification[20], but adapted to unidimensional signals. This architecture allows deep neural networks to be efficiently trained by including skip connections. We have adopted the modification in the residual block proposed by He et. al.[36].

All ECG recordings, which have between 7 and 10 seconds of duration and are sampled at frequencies ranging from 300 to 1000Hz, are re-sampled to 400 Hz and zero-padded, resulting in signals of fixed length (4096 samples), which are fed to the neural network. The output is the age-predicted for that given exam.

The network consists of a convolutional layer followed by 5 residual blocks with two convolutional layers per block. The output of each convolutional layer is rescaled using batch normalization[37] and fed into a rectified linear activation unit ReLU. Dropout[38] is applied after the nonlinearity. The convolutional layers have filter length 17, starting with 4096 samples and 64 filters for the first layer and residual block and increasing the number of filters by 64 and subsampling by a factor of 4 every residual block. Max Pooling[39] and convolutional layers with filter length 1 are included in the skip connections to make the dimensions match those from the signals in the main branch.

The weighted mean square error is minimized using Adam optimizer[40] with default parameters and a learning rate of 0.001. The learning rate is reduced by a factor of 10 whenever the validation loss does not present any improvement for 7 consecutive epochs. The neural network weights were initialized sampling from a normal random variable scaled as in He et. al.[41] and the bias was initialized with zeros. The training runs for 70 epochs with the final model being the one with the best validation results during the optimization process.

Cardiologist assessment of ECG-age from the tracings

To assess whether ECG-age was capturing ECG changes that are recognizable to medical doctors, we conducted an additional experiment asking three experienced medical doctors to identify, in paired ECGs, ECG tracings associated with having higher ECG-age. All ECGs considered were normal ECGs from the CODE cohort. Within each pair of equal chronological age and sex, one individual had an ECG-age more than 8 years greater than their chronological age and the other had an ECG-age more than 8 years smaller than their chronological age. We included one pair of male and one pair of female patients for each age between 16 and 85 (whenever possible), totaling 134 pairs. At the edges of our age-range, it was not always possible to have an ECG tracing with ECG-age more than 8 years smaller than the chronological age paired with a tracing with ECG-age more than 8 years smaller than the chronological age, and, in these situations, we use tracings associated with ECG-ages within the 8 years range of the patient‘s chronological age. The experiment was divided into three stages where doctors annotated 44, 45, and 45 pairs of ECGs tracings respectively. In stages 1 and 3, doctors were not given the answer after accomplishing the task, and in stage 2 they were. The idea behind this distinction is to see whether doctors would fare any better after a round with explicit feedback on their performance.

Saliency maps in the time and frequency domain

We performed an analysis to assess the relative importance of different segments of the ECG trace in the age prediction. The results are displayed in Supplementary Fig 1 and the relative size of the blue disks in the image might be interpreted as the relative importance of each point to the output prediction (at least in terms of the linearized local analysis). Similar approaches have been pursued in the interpretation of other DNN-based ECG predictors[8,42]. Here we use a rather straightforward procedure for generating the saliency maps[21]: the raw ECG tracing is fed to the deep neural network and the ECG-age is computed. Using backpropagation we compute the derivative of the ECG-age with respect to each point. We then generate transparent blue disks in the same plot as the ECG-tracing, where the size of these disks is proportional to the magnitude of the derivative in this point. This procedure results in the saliency map displayed in **Supplementary Fig 1**.

In **Supplementary Fig 2,** we show a similar analysis, but now in the frequency domain. We take the discrete Fourier transform of the gradients computed as described above. We do that for 100 ECG exams, sampled at random, from the ECG exams classified as normal in each of the three different cohorts (CODE-15%, ELSA-Brasil and SaMi-Trop) and show the median and interquartile range in the Figure.

Statistical analysis

To assess the performance of the DNN model in the CODE-15%, ELSA-Brasil and SaMi-Trop cohorts, we computed the R square metric using linear regression and calculated the mean absolute error (MAE) using the chronological age. For further analysis, we divided the samples in three groups, based in differences between predicted ECG-age and chronological age: those with ECG-age more than 8 years smaller than the

chronological age, those with ECG-age within a range of 8 years from their chronological age, and those ECG-age more than 8 years greater than the chronological age.

For mortality analysis, we used Cox proportional regression model, reporting hazard ratios (HR) and 95% confidence intervals (95%CI). The analysis was performed in all ECGs of the three cohorts, with two levels of adjustments: age and sex; age, sex, and other cardiac risk factors (hypertension, diabetes mellitus, smoking). Other two models in the second level of adjustment including dyslipidemia, for CODE-15% and ELSA-Brasil, and obesity, only for ELSA-Brasil, were fitted. A second mortality analysis with the same parameters, was performed considering only normal ECGs from CODE-15% (n=80679) and ELSA-Brasil (n=7691) cohorts. The proportional hazard assumption was verified using a log (-log (survival)) plot and Schoenfeld residuals. We also performed the mortality analysis for CODE-15%, dividing the samples into five groups according to quintiles of the difference of ECG-age and chronological age, showing the adjusted survival curves and HRs from the adjusted Cox models by age and sex. The area under the receiver operating characteristic curve (AUC) was used to evaluate the Cox model performance for 1-year mortality risk prediction.

To explore the association of risk factors with the ECG-age being more than 8 years greater than the chronological age we performed a logistic regression analysis for the ELSA-Brasil cohort including all ECG and only subjects with normal ECG. In this analysis we fitted a model for each risk factor adjusted by age and sex and reported the ORs and 95% confidence intervals.

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Contribution statement

E.M.L., G.M.M.P., A.H.R., T.B.S. and A.L.R. were responsible for the study design. A.L.R. conceived the project and acted as the project leader. A.H.R. choosed the neural network architecture, implemented and tuned the deep neural network. E.M.L did the survival analysis and all the statistical tests. G.M.M.P. and A.L.R. interpreted the results and provided clinical interpretation. A.H.R., D.M.O., P.R.G. were responsible for preprocessing the training data. P.R.G was responsible for maintaining and extracting the CODE database. M.M.P.F, E.C.S., S.M.B., L.G., B.B.D. were responsible for cohort design and management, data acquisition, follow-up and ECG exams in ELSA-Brasil and Sami-Trop cohorts. G.M.M.P., A.H.R., E.M.L., W.M.Jr., T.B.S. and A.L.R. contributed to the writing and all authors revised it critically for important intellectual content. All authors read and approved the submitted manuscript.

Competing interests:

None of the authors have financial and non-financial competing interests.

Data Availability:

SaMi-Trop cohort was made openly available (https://doi.org/10.5281/zenodo.4905618). The CODE-15% cohort was also made openly available (https://doi.org/10.5281/zenodo.4916206) The datasets contain information about mortality, age, sex, the ECG tracings and the flag indicating whether the ECG tracing is normal. The DNN model parameters that give the results presented in this paper are also available (https://doi.org/10.5281/zenodo.4892365). This should allow the reader to partially reproduce the results presented in the paper. Restrictions apply to additional clinical information on the CODE-15% and SaMi-Trop cohorts; to the full CODE cohort; and, to the ELSA-Brasil cohort. Researchers affiliated to educational or research institutions might make requests to access the datasets. Requests should be made to the corresponding author of this paper. They will be forwarded and considered on an individual basis by the Telehealth Network of Minas Gerais and by ELSA-Brasil Steering Committee. An estimate for the time needed for data access requests to be evaluated is three months. If approved, any data use will be restricted to non-commercial research purposes. The data will only be made available on the execution of appropriate data use agreements.

Code Availability:

The code for the model training, evaluation and statistical analysis is available at the github repository https://github.com/antonior92/ecg-age-prediction (the release at the time of submission was archived in https://doi.org/10.5281/zenodo.4975439 43).

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7. CONSIDERAÇÕES FINAIS

Conforme a Organização Mundial de Saúde, a atenção primária à saúde é parte integral do sistema de saúde de um país, com enfoque principal no desenvolvimento social e econômico da comunidade(78). É o primeiro nível de contato do indivíduo com sistema nacional de saúde, levando atenção multiprofissional para próximo da sua residência. Constitui o filtro capaz de organizar o fluxo dos serviços nas redes de saúde, dos mais simples aos mais complexos(79). Sua essência é tratar das pessoas e não de doenças e condições específicas. Ações relativas à promoção à saúde e prevenção tanto primária e secundária de doenças cardiovasculares são necessárias para melhoria da saúde coletiva.

Há uma busca constante no meio científico para a identificação de variáveis, clínicas ou obtidas por meio de exames complementares, que sejam capazes de definir o risco cardiovascular do paciente e, consequentemente, promover ações para a prevenção de eventos(23). O uso do escore de cálcio coronariano, ecodoppler de carótidas e vertebrais e dosagem sérica de proteína C reativa ultrassensível são exemplos de exames já indicados para os pacientes de risco intermediário cardiovascular(80). No entanto, o custo-benefício desses procedimentos é questionável(80), principalmente, no contexto de saúde pública.

Outra questão importante a ser apontada é a incorporação dos tradicionais escores de risco cardiovasculares, como: *Framingham*(81) ou da *American Heart Association*(82), na população brasileira(83). Sua aplicabilidade possui limitações devido à nossa ampla diversidade socioeconômica e racial. Escores de risco com validação na nossa comunidades são importantes, principalmente, com o uso de exames acessíveis, de baixo custo, não invasivos e eficazes.

O ECG possibilita a identificação de pacientes com maior risco de mortalidade.

O diagnóstico de algumas anormalidades eletrocardiográficas, como: BRE, BRD e BAV, implica em maior mortalidade para o paciente, independentemente da sua idade, sexo ou comorbidades prévias. Além disso, a introdução da idade eletrocardiográfica como ferramenta de auxílio nas decisões clínicas é promissora.

O conceito de idade biológica já foi avaliado em outros cenários, com o uso de exames laboratoriais e dados clínicos(84). A possibilidade de uma nova informação clínica, proveniente de um exame simples e de baixo custo, como a idade eletrocardiográfica é animadora. Na prática, esse dado, que é um resumo de características eletrocardiográficas individuais, significa de maneira simples e intuitiva o risco cardiovascular do paciente. É uma informação acessível e compreensível para o leigo e que, talvez, traga maior envolvimento do paciente no seu tratamento do que um simples nível de colesterol ou o diagnóstico de bloqueio de ramo. Além disso, a idade eletrocardiográfica possui significado prognóstico, inclusive em ECG normais, o que agrega mais uma informação ao exame que, anteriormente, seria negligenciada pelos métodos tradicionais de avaliação eletrocardiográfica.

A estratificação do risco cardiovascular pela idade do ECG também é ferramenta potencialmente útil para a prática clínica, principalmente na atenção primária à saúde. Identificar o paciente que se beneficiará de um controle mais rigoroso de pressão arterial, diabetes e dos níveis de colesterol pode prevenir, futuramente, eventos cardíacos.

As alterações eletrocardiográficas sinalizam para a equipe de saúde da família a potencial gravidade do paciente e a importância do tratamento adequado das comorbidades associadas. Além disso, auxiliam na racionalização e definição de prioridade dos encaminhamentos para os centros de referência secundários ou terciários.

No Brasil, um país de dimensões continentais com índices de desenvolvimento humano extremamente heterogêneos conforme a região, estratégias para a equalização da assistência à saúde devem ser consideradas, como: implementação da telessaúde e o uso da IA.

O telediagnóstico possibilita a realização de exames em locais remotos com laudos por especialistas à distância, sem a necessidade de deslocamento do paciente. A tele-educação permite capacitação multiprofissional continuada, com enfoque nas necessidades de cada região, valorizando o profissional da atenção primária à saúde. Com a pandemia do COVID-19, as modalidades de teleconsultoria e teleconsulta (recentemente aprovada pelo Conselho Federal de Medicina) ficaram ainda mais em evidência.

A impossibilidade de deslocamento dos pacientes revelou um problema antigo da centralização e da desigualdade de acesso aos serviços médicos, principalmente especializados. A teleconsultoria, que consiste na discussão entre profissionais de saúde sobre um paciente, auxilia muito a atenção primária e evita encaminhamentos dispensáveis ou propedêuticas fúteis que oneram o sistema, sem beneficio ao usuário. A teleconsulta, principalmente em algumas especialidades clínicas, como: psiquiatria e dermatologia, consegue suprir a demanda de alguns pacientes e racionalizar o atendimento médico.

A IA é de grande valia para o manuseio de bases de dados consolidadas com enorme volume de informações (*big data*), em que há uma limitação do uso das técnicas convencionais de estatística. Apesar do desenvolvimento tecnológico dos modelos de ML ser complexo, a sua aplicabilidade prática é simples e acessível. Já consumimos serviços de IA sem a nossa percepção, como em sistema de bancos, buscas pela internet e redes sociais. Sua incorporação na área da saúde deve ser

encarada como uma ferramenta valiosa para melhoria da assistência. Com a digitalização dos prontuários eletrônicos e exames complementares, o desenvolvimento dos modelos de ML para predição e diagnóstico de doenças se encontra em crescimento exponencial. Esses modelos facilitam processos, reduzem custos e auxiliam os profissionais de saúde na tomada de decisão clínica.

No contexto de saúde pública, o real conhecimento dos dados epidemiológicos possibilita a estruturação de políticas de saúde. O direcionamento adequado dos recursos financeiros conforme a realidade de cada população, a implementação de ações para a educação da comunidade em saúde, a disponibilização de diretrizes assistenciais para a equipe de saúde da família, o acesso racional e eficaz aos serviços de saúde secundários e terciários e a incorporação de novas tecnologias, como a IA são estratégias a serem planejadas e adotadas para melhoria da qualidade da saúde coletiva.

8. CONCLUSÕES

Marcadores eletrocardiográficos foram preditores de mortalidade na população da RTMG. BRE, BRD, BAV foram associados a maior risco de morte por todas as causas, independentemente da idade, sexo e comorbidades associadas. BRE foi preditor independente de maior mortalidade cardiovascular. Pré-excitação ventricular e BAV de segundo grau Mobitz I não foram associados a maior mortalidade geral.

Nos pacientes dos estudos CODE, ELSA-Brasil e SaMi-Trop, a idade eletrocardiográfica superior a 8 anos da idade cronológica foi preditor independente de mortalidade geral. Apenas nos pacientes do estudo CODE e ELSA-Brasil, a idade eletrocardiográfica inferior a 8 anos da cronológica foi fator protetor, independentemente da idade, sexo e comorbidades, para morte por todas as causas.

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