UNIVERSIDADE FEDERAL DE ALAGOAS
FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS

Felipe Camilo Santiago Veloso

Escore de predição de óbito neonatal no quinto minuto de vida

Maceió – AL
2022

FELIPE CAMILO SANTIAGO VELOSO

Escore de predição de óbito neonatal no quinto minuto de vida

Dissertação de Mestrado apresentada ao Programa de Pós-Graduação em Ciências Médicas da Universidade Federal de Alagoas (UFAL), como parte das exigências para a obtenção do título de Mestre em Ciências Médicas.

Área de Concentração: Doenças crônicas e degenerativas.

Orientador: Prof. Dr. Samir Buainain Kassar.
Coorientador: Prof. Dr. Jorge Artur Peçanha de Miranda Coelho.

Maceió – AL

2022

Catalogação na Fonte
Universidade Federal de Alagoas
Biblioteca Central
Divisão de Tratamento Técnico
Bibliotecário: Marcelino de Carvalho Freitas Neto – CRB-4 – 1767

V443e Veloso, Felipe Camilo Santiago.
Escore de predição de óbito neonatal no quinto minuto de vida / Felipe Camilo Santiago Veloso. – 2022.
69 f. : il.

Orientador: Samir Buainain Kassar.
Coorientador: Jorge Arthur Peçanha de Miranda Coelho.
Dissertação (Mestrado em Ciências Médicas) – Universidade Federal de Alagoas. Faculdade de Medicina. Programa de Pós-Graduação em Ciências Médicas. Maceió, 2022.
Inclui produto educacional.

Bibliografia: f. 42-46.
Apêndices: f. 47-48.
Anexos: f. 49-69.

1. Mortalidade neonatal. 2. Fatores de risco. 3. Regras de decisão clínica. I. Título.

CDU: 618.333

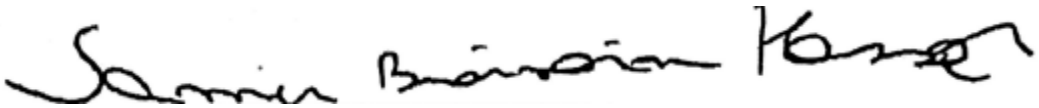
FELIPE CAMILO SANTIAGO VELOSO

Escore de predição de óbito neonatal no quinto minuto de vida

Dissertação de Mestrado apresentada ao Programa de Pós-Graduação em Ciências Médicas da Universidade Federal de Alagoas (UFAL), como parte das exigências para a obtenção do título de Mestre em Ciências Médicas.

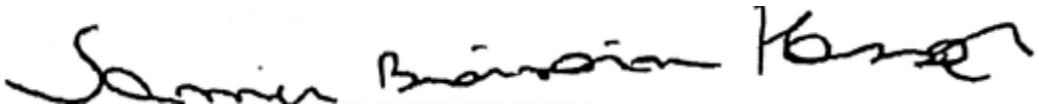
Área de Concentração: Doenças crônicas e degenerativas.

Orientador: Prof. Dr. Samir Buainain Kassar.
Coorientador: Prof. Dr. Jorge Artur Peçanha de Miranda Coelho.

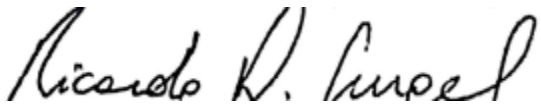


Prof. Dr. Samir Buainain Kassar, CPF: 384.145.544-15, Universidade Federal de Alagoas. (Orientador)

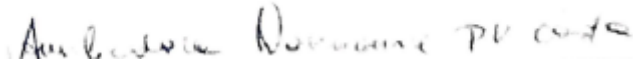
BANCA EXAMINADORA



Prof. Dr. Samir Buainain Kassar, CPF: 384.145.544-15, Universidade Federal de Alagoas. (Orientador)



Prof. Dr. Ricardo Queiroz Gurgel, CPF: 154.049.605-82, Universidade Federal de Sergipe. (Avaliador Externo)



Profa. Dra. Auxiliadora Damianne Pereira Vieira da Costa, CPF: 034.537.184-45, Universidade Federal de Alagoas. (Avaliador Interno)

Prof. Dr. Alysson Wagner Fernandes Duarte, CPF: 056.482.824-60, Universidade Federal de Alagoas. (Avaliador Interno)

RESUMO

O estudo objetiva elaborar um escore de predição de óbito neonatal. Trata-se de um estudo caso-controle que utilizou dados secundários públicos coletados a partir do Sistema de Informação sobre Nascidos Vivos (SINASC) e do Sistema de Informações sobre Mortalidade (SIM). O espaço temporal foi cinco anos (2016 – 2020). Considerou-se controle os dois nascidos-vivos registrados imediatamente após a ocorrência do óbito (caso). As variáveis foram idade gestacional, peso ao nascer, número de consultas pré-natais, Apgar no 5º minuto e anomalias congênitas. As análises foram compostas pela frequência absoluta e relativa, Odds Ratio Bruto (ORB) e Odds Ratio Ajustado (ORA). Para a construção do escore de predição, calculou-se o ponto de corte, sensibilidade, especificidade, razão de probabilidade positiva (RPP), razão de probabilidade negativa (RPN) e área sob a curva (ASC). O peso < 2500 gramas obteve um ORA de 7.56 (5.86, 9.74), a presença de malformação ORA 28.15 (16.73, 47.36), a idade gestacional < 37 semanas ORA 6.06 (4.72, 7.78), o Apgar < 7 no 5º minuto ORA 61.61 (38.01, 99.88) e número de consultas pré-natais < 7 ORA 1.29 (1.04, 1.59). O ponto de corte do escore de predição foi cinco pontos, sensibilidade 70.21%, especificidade 96.65%, RPP 20.95, RPN 0.30 e AUC 0.896. O escore de predição mostra-se promissor para predizer o óbito neonatal, apresentando uma grande influência na probabilidade quando maior que cinco pontos, obtendo melhor pontuação quando positiva.

PALAVRAS-CHAVE: Mortalidade neonatal. Fatores de risco. Regras de predição clínica.

ABSTRACT

The study aims to develop a neonatal death prediction score**.** This is a case-control study that used public secondary data collected from the Live Births Information System (LBIS) and the Mortality Information System (MIS). The time span was five years (2016 – 2020). The two live births registered immediately after the occurrence of death (case) were considered control. The variables were gestational age, birth weight, number of prenatal consultations, 5th minute APGAR and congenital anomalies. The analyzes consisted of absolute and relative frequency, Crude Odds Ratio (COR) and Adjusted Odds Ratio (AOR). To construct the prediction score, the cutoff point, sensitivity, specificity, positive probability ratio (PPR), negative probability ratio (NPR) and area under the curve (AUC) were calculated. Weight < 2500 grams had an AOR of 7.56 (5.86, 9.74), the presence of malformation AOR 28.15 (16.73, 47.36), gestational age < 37 weeks AOR 6.06 (4.72, 7.78), the Apgar < 7 at the 5th minute AOR 61.61 (38.01, 99.88) and number of prenatal consultations < 7 AOR 1.29 (1.04, 1.59). The prediction score cutoff was five points, sensitivity 70.21%, specificity 96.65%, PPR 20.95, NPR 0.30 and AUC 0.896**.** The prediction score is promising to predict neonatal death, showing a great influence on the probability when greater than five points, obtaining a better score when positive.

KEYWORDS: Neonatal mortality. Risk factors. Clinical Decision Rules.

SUMÁRIO

1 INTRODUÇÃO

O óbito neonatal consiste na morte entre o nascimento e o 27º dia de vida (PATHIRANA et al, 2016). Tal período é comumente dividido em óbito neonatal precoce e tardio, cada um com suas particularidades causais e importância epidemiológica (VELOSO et al, 2019).

No primeiro período, entre o nascimento e o 7º dia de vida, estão incluídas as causas evitáveis, sendo a prematuridade, baixo peso ao nascer e complicações intraparto os motivos mais prevalentes (VELOSO et al, 2019; VALLELY et al, 2021). Já no segundo período, são as anomalias congênitas as causas mais prevalentes (VALLELY et al, 2021).

A primeira semana de vida é a mais crítica para o recém-nascido, principalmente nas primeiras 24 horas de vida (LEHTONEN, 2017). Estima-se que, anualmente, 2.7 milhões de óbitos neonatais ocorram em todo mundo, sendo 1 milhão deles acontecendo na primeira semana (LEHTONEN, 2017; VALLELY et al, 2021).

Diante disso, é importante a utilização de ferramentas para auxiliar na prevenção desses óbitos, uma vez que são, em sua maioria, causas evitáveis (DORLING; FIELD; MANKTELOW, 2005; PEDROSA et al, 2007; VELOSO et al, 2019). Há, na literatura, inúmeras propostas de escores de predição, sejam para países de alta, média ou baixa renda, sejam para ambientes hospitalares ou em unidades intensivas neonatais (INTERNATIONAL NEONATAL NETWORK, 1993; DORLING; FIELD; MANKTELOW, 2005; ROSENBERG et al., 2008; MEDVEDEV et al., 2020).

O Brasil, um país de dimensões continentais, possui diversos contextos sociais e econômicos. O Nordeste encontra-se nesse contexto como uma região com dificuldades assistenciais e isso se reflete nos altos números de óbitos neonatais. É, sim, possível evitar esses óbitos por meio da assistência e da prevenção, as quais podem ser realizadas tanto por meio de políticas públicas, quanto por ferramentas capazes de predizer o óbito.

Há várias escores de predição disponíveis e específicos para as diversas situações e realidades. Porém, um escore de predição com dados brasileiros auxiliaria a anteceder os desfechos desfavoráveis no Brasil, tornando-se, assim, interessante a elaboração de um escore de prevenção de óbito neonatal a fim de auxiliar os profissionais de saúde a entender e prever o óbito neonatal no Brasil.

2 OBJETIVOS

2.1 Objetivo geral

Elaborar um escore de predição de óbito neonatal utilizando dados coletados a partir do Sistema de Informação sobre Nascidos Vivos (SINASC) e do Sistema de Informações sobre Mortalidade (SIM).

2.2 Objetivos específicos

Analisar a ocorrência de óbitos neonatais a partir das variáveis idade gestacional; peso ao nascer; número de consultas pré-natais; Apgar no 5º minuto e anomalias congênitas.

Analisar o risco de ocorrência de óbito neonatal a partir das variáveis idade gestacional; peso ao nascer; número de consultas pré-natais; Apgar no 5º minuto e anomalias congênitas.

3 REVISÃO DE LITERATURA

3.1 Definição de óbito neonatal

O óbito neonatal ocorre entre o nascimento e o 27º dia de vida (ISLAM; BISWAS, 2021). Há dois momentos bem definidos que auxiliam o profissional de saúde a entender a dinâmica desse período (BELUZO et al., 2020). O óbito neonatal precoce, compreendido entre o nascimento e o 7º dia de vida, é o período mais importante dessa divisão (LIMA et al., 2020). É nesse momento que, geralmente, são encontrados os fatores evitáveis, cuja ação dos profissionais de saúde na prevenção é essencial para diminuir as chances de óbito (PEDROSA et al. 2007; VELOSO et al., 2019). Já no óbito neonatal tardio, período entre o 7º e o 27º dia de vida, estão situadas as causas mais prolongadas, cuja prevenção não é o fator essencial na redução dos números, mas sim o tratamento eficaz (PEDROSA et al. 2007; LANSKY et al, 2014; LIMA et al., 2020).

3.2 Fatores relacionados ao óbito neonatal

Os fatores relacionados ao óbito neonatal podem ser divididos de acordo com a evitabilidade causal (PEDROSA et al. 2007). As causas evitáveis são fatores modificáveis a partir de mudanças individuais e governamentais (VELOSO et al., 2019). O óbito evitável é um reflexo da saúde pública de um país, sinônimo de uma falha na prevenção ou da assistência ao recém-nascido (PEDROSA et al. 2007; LANSKY et al, 2014; VELOSO et al., 2019).

3.3 Epidemiologia

Entre 2000 e 2020, a média global geral foi de 65.267.392 óbitos neonatais (UNICEF, 2020). Apesar desse número expressivo, ao comparar os números no início e no término do período, houve uma redução de, aproximadamente, 40% nos óbitos neonatais, mostrando que houve uma importante mudança no contexto da prevenção e da assistência a essa problemática (UNICEF, 2020).

Entre 1999 e 2019, o Brasil registrou 659.543 óbitos neonatais em 20 anos, sendo 506.655 óbitos neonatais precoces e 152.888 óbitos neonatais tardios (BRASIL, 2021). A região Sudeste foi a região mais afetada com 236.636 óbitos neonatais, sendo 176.241 precoces e 60.395 tardios (BRASIL, 2021). Logo em seguida, a região Nordeste registrou 222.518 óbitos neonatais, sendo 177.203 precoces e 45.315 tardios (BRASIL, 2021).

Em Alagoas, baseando-se nas regiões de saúde, de 1999 a 2019, a 1ª Região de Saúde, na qual a capital Maceió está situada, foi registrado 5.439 óbitos neonatais, sendo 4.186 precoces e 1.253 tardios (BRASIL, 2021).

3.4 Escores de Predição

Os escores de predição são ferramentas de pontuação que envolvem o uso de dados demográficos, fisiológicos e clínicos para quantificar uma determinada questão investigada (DORLING; FIELD; MANKTELOW, 2005).

Há, classicamente, seis escores que avaliam o risco de óbito neonatal: *Clinical Risk Index for Babies* (CRIB); *Clinical Risk Index for Babies* II (CRIB II); *Score for Neonatal Acute Phisiology* (SNAP); *Score for Neonatal Acute Phisiology* II (SNAP II); *Score for Neonatal Acute Phisiology – Perinatal Extension* (SNAPPE); e *Score for Neonatal Acute Phisiology – Perinatal Extension* II (SNAPPE II). (MCLEOD et al, 2020).

O CRIB, descrito em 1993, consiste em uma coorte composta por 812 recém-nascidos de muito baixo peso ao nascer ou prematuros extremos tratados em uma Unidade de Terapia Intensiva Neonatal (UTIN) no Reino Unido, e combinou o peso ao nascer, a idade gestacional, a presença de malformação congênita, o valor máximo do *base excess* nas primeiras 12 horas de vida e o valor mínimo e máximo do FiO2 nas primeiras 12 horas de vida, sendo classificados como um escore de boa qualidade discriminatória (ASC = 0.90). (INTERNATIONAL NEONATAL NETWORK, 1993).

O SNAP, uma coorte de 1643 recém-nascidos tratados em três UTINs em Boston (EUA), foi desenvolvido no mesmo ano do CRIB, e utilizou 26 variáveis escolhidas arbitrariamente e analisadas nas primeiras 24 horas. Tais variáveis consistiram na pressão arterial, frequência cardíaca, frequência respiratória, temperatura, PO2 e razão PO2/FiO2. (RICHARDSON et al., 1993). O SNAPPE, por sua vez, ampliou a análise do SNAP, adicionando fatores perinatais, a exemplo do peso ao nascer, idade gestacional e Apgar no 5º minuto. (RICHARDSON et al., 1993). Da mesma forma que o CRIB, tanto o SNAP quanto o SNAPPE consistiram em um escore de boa qualidade discriminatória (ASC SNAP = 0.87; ASC SNAPPE = 0.90). (DORLING; FIELD; MANKTELOW, 2005).

O SNAP II e o SNAPPE II foram coortes lançadas em 2001 com o objetivo de simplificar a abordagem dos escores originais (RICHARDSON et al., 2001). O SNAP II utilizou a pressão arterial média, a menor temperatura aferida, a razão PO2/FiO2, o menor pH sérico, a presença de múltiplos desmaios e a diurese nas primeiras 12 horas de vida

(RICHARDSON et al., 2001). Já o SNAPPE II, além das variáveis do SNAP II, utilizou o peso menor que 749 gramas, o Apgar menor que 7 no 5º minuto e a relação peso – idade gestacional. (RICHARDSON et al., 2001).

O CRIB II, coorte construída em 2003, surgiu a partir de críticas em relação à primeira versão, as quais se resumem à influência do cuidador no fornecimento das informações a serem coletadas e contemplam as variáveis peso ao nascer (ultrassonografia gestacional), sexo, temperatura na admissão e o valor do *base excess* nas primeiras 12 horas de vida (PARRY et al., 2003)

No decorrer do tempo, surgiram outros escores para ampliar os parâmetros dos escores clássicos, bem como solucionar problemas relacionados à localidade ou ao acesso à saúde, a exemplo do *Neonatal Mortality Score from Ethiopia* (NMSE), *Neonatal del Cono Sur Score* (NEOCOSUR) e *Neonatal Mortality Score-9 Mexico* (EMN-9 Mex).

O NMSE, foi conduzido a partir de um caso-controle, sendo 124 casos (óbitos neonatais) e 122 controles (sobreviventes). Os parâmetros utilizados foram a idade materna, a paridade, o sexo, a idade gestacional, o peso ao nascer, o tipo de parto, além da frequência cardíaca, respiratória, temperatura, presença de desconforto respiratório, nível de consciência, relação peso – idade gestacional e perímetro cefálico, produzindo um ASC de 0.88. (MEDIRATTA et al., 2020)

O NEOCOSUR, uma coorte prospectiva, a qual utilizou dados de 16 unidades neonatais na América do Sul, lançou-se como uma boa proposta para países de média e baixa renda, utilizando como parâmetros a idade materna, o peso ao nascer, idade gestacional, Apgar no 1º minuto, malformações congênitas, sexo, uso de corticoide no período perinatal e a relação peso – idade gestacional. O escore em questão encontrou um ASC de 0.85. (MARSHALL et al., 2005).

O EMN-9 Mex é um caso-controle aninhado, o qual utilizou 22 casos e 132 controles e selecionou como parâmetros: peso ao nascer, presença de acidose metabólica, nível de lactato, razão PaO2 / FiO2, contagem de plaquetas e glicemia, encontrando um ASC de 0.92. (MÁRQUEZ-GONZÁLEZ et al., 2015). Seguindo a mesma tendência e proposta dos escores, surgiram o *Simplified Age-Weight-Sex* (SAWS) e o *Neonatal Mortality Risk among neonates weighing 2000 g or less* (NMR-2000).

O SAWS, uma variável do CRIB-II, foi construída a partir de uma coorte retrospectiva utilizando 467 recém-nascidos no Cairo (Egito). Com a proposta de ser utilizado principalmente em países de baixa renda, o SAWS utiliza a peso ao nascer, idade gestacional e sexo, com um ASC de 0.71 (ROSENBERG et al., 2008). Já o NMR-2000,

também construída a partir de uma coorte retrospectiva, utilizou os dados de 187 unidades neonatais do Reino Unido e da Gâmbia. Com uma proposta de ser utilizado em países de média e baixa renda, o escore utiliza o peso ao nascer, a saturação de oxigênio e o suporte de oxigênio nas primeiras 24 horas de vida, produzindo um ASC de 0.85 (MEDVEDEV et al., 2020).

A tabela 1 resume as principais características dos 11 escores de predição de óbito neonatal.

Tabela 1 - Principais características dos 11 escores de predição de óbito neonatal.

ESCORE	ANO	TIPO DE ESTUDO	VARIÁVEIS PRINCIPAIS
CRIB	1993	Coorte	Peso ao nascer; Idade gestacional; Presença de malformação congênita; Valor máximo do *base excess* nas primeiras 12 horas de vida; Valor mínimo e máximo do FiO2 nas primeiras 12 horas de vida
CRIB II	2003	Coorte	Peso ao nascer (Ultrassonografia gestacional); Sexo; Temperatura na admissão; Valor do *base excess* nas primeiras 12 horas de vida
SNAP	1993	Coorte	Pressão arterial; Frequência cardíaca; Frequência respiratória; Temperatura; PO2 e Razão PO2/FiO2
SNAP II	2001	Coorte	Pressão arterial média; Menor temperatura aferida; Razão PO2/FiO2; Menor pH sérico; Presença de múltiplos desmaios; Diurese nas primeiras 12 horas de vida
SNAPPE	1993	Coorte	SNAP + Peso ao nascer; Idade gestacional; Apgar no 5º minuto
SNAPPE II	2001	Coorte	SNAP II + Presença de peso menor que 749 gramas; Apgar menor que 7 no 5º minuto; Relação peso – idade gestacional
NMSE	2020	Caso-Controle	Idade materna; Paridade; Sexo; Idade gestacional; Peso ao nascer; Tipo de parto; Frequência cardíaca; Frequência Respiratória; Temperatura; Presença de desconforto respiratório; Nível de consciência; Relação peso – idade gestacional; perímetro cefálico
NEOCOSUR	2005	Coorte	Idade materna; Peso ao nascer; Idade gestacional; Apgar no 1º minuto; Malformações congênitas; Sexo; Uso de corticoide no período perinatal; Relação peso – idade gestacional
EMN-9-MEX	2015	Caso-Controle Aninhado	Peso ao nascer; Presença de acidose metabólica; Nível de lactato; Razão PaO2/FiO2; Contagem de plaquetas; Glicemia
SAWS	2008	Coorte	Peso ao nascer; Idade gestacional; Sexo
NMR-2000	2020	Coorte	Peso ao nascer; Saturação de oxigênio; Suporte de oxigênio nas primeiras 24 horas de vida

Fonte: elaborado pelos autores.

4 JUSTIFICATIVA

O Brasil, um país de dimensões continentais, possui diversos contextos sociais e econômicos. Tal fato reflete na condição assistencial ao recém-nascido, sendo mais favorável a sobrevivência em regiões mais desenvolvidas. O Nordeste encontra-se nesse contexto, como uma região com dificuldades assistenciais.

O óbito neonatal precoce é o fator causal predominante do óbito neonatal brasileiro, indicando que é possível evitar esses óbitos por meio da assistência e da prevenção, as quais podem ser realizadas tanto por meio de políticas públicas, quanto por ferramentas capazes de predizer o óbito.

Há várias escores de predição disponíveis e específicos para as diversas situações e realidades. O escore mais completo atualmente é o NMR-2000, o qual utiliza três parâmetros e possui uma alta acurácia (ASC 0.85). Há também o SAWS, específico para países de média e baixa renda, o qual poderia ser utilizado no Brasil. Apesar dessas possibilidades, é visto a necessidade de ampliar as variáveis utilizadas no SAWS, porém com uma metodologia semelhante ao NMR-2000. Por isso, diante desse contexto, a proposta desse estudo é elaborar um escore de predição de óbito neonatal a fim de auxiliar os profissionais de saúde a entender e predizer o óbito neonatal no Brasil.

5 METODOLOGIA

5.1 Tipo de estudo

Estudo caso-controle o qual utilizou dados secundários públicos coletados do Sistema de Informação sobre Nascidos Vivos (SINASC) e do Sistema de Informações sobre Mortalidade (SIM).

5.2 Local e Amostra do estudo

Mediante autorização da Superintendência de Vigilância em Saúde (SUVISA) da Secretaria de Saúde do Estado de Alagoas (SESAU), número do processo 02000.0000025417/2020, os pesquisadores coletaram os dados do Estado de Alagoas *in locu*, diminuindo, assim, a possibilidade de erros ao coletar estas informações via Departamento de Informática do Sistema Único de Saúde do Brasil (DATASUS).

Considerou-se caso os óbitos neonatais e os controles os dois nascidos-vivos registrados imediatamente após a ocorrência do óbito.

5.3 Critérios de elegibilidade

5.3.1 Critérios de inclusão

Todos os óbitos neonatais ocorridos em Alagoas (Brasil) entre janeiro de 2016 e outubro de 2020 foram incluídos, bem como os dois nascidos-vivos registrados imediatamente após esses óbitos neonatais.

5.3.2 Critérios de exclusão

Excluíram-se os registros de óbitos neonatais, bem como de nascidos-vivos, os quais não possuíam informações a respeito do peso ao nascer, da idade gestacional, do Apgar no 5º minuto, do número de consultas pré-natais ou da presença de anomalia congênita.

5.4 Coleta e Armazenamento de dados

A coleta de dados foi realizada por cinco pesquisadores utilizando um software desenvolvido pelo Departamento de Estatística da Universidade Federal de Alagoas, construído exclusivamente para este projeto. O software utilizou um script em linguagem Python versão 3.8.8 (Python Software Foundation, Delaware, EUA) e uma biblioteca de manipulação de dados tabulares pandas versão 1.2.3 (Python Software Foundation, Delaware, EUA).

O processo de acesso aos dados consistiu na realização de um *Linkage*. A partir do número de registro da DNV, encontrou-se a DO correspondente, bem como as duas DNV subsequentes a hora do óbito registrada na DO anteriormente coletada.

Após o encontro das informações, os dados foram importados para uma planilha construída a partir do software Microsoft Excel 365 (Microsoft Corporation, Redmond – Washington, EUA).

Szwarcwald *et al*. (2019), analisando as informações do Sistema de Informações sobre Nascidos Vivos (SINASC), principal base de dados utilizada em nosso estudo, mostraram que houve concordância em todas as variáveis testadas, sendo a variável de maior fragilidade a idade gestacional com valor de *kappa* de 0.461, reforçando a confiabilidade desses dados.

5.6 Variáveis

5.6.1 Primária

A variável primária foi o óbito neonatal, uma variável qualitativa dicotômica.

5.6.2 Secundárias

5.6.2.1 Caso

a) **semanas de gestação** (menor que 37 semanas, maior ou igual a 37 semanas), variável qualitativa dicotômica;

b) **peso ao nascer** (menor que 2.500 g, maior ou igual a 2.500 g), variável qualitativa dicotômica;

c) **números de consultas pré-natais** (número de consultas menor que 7, número de consultar maior ou igual a 7), variável qualitativa dicotômica;

d) **valor do Apgar no 5º minuto** (Apgar menor que 7, Apgar maior ou igual a 7), variável qualitativa dicotômica;

e) **presença de anomalia** (presença, ausência ou ignorado), variável qualitativa nominal.

5.6.2.2 Controle

a) **semanas de gestação** (menor que 37 semanas, maior ou igual a 37 semanas), variável qualitativa dicotômica;

b) **peso ao nascer** (menor que 2.500 g, maior ou igual a 2.500 g), variável qualitativa dicotômica;

c) **números de consultas pré-natais**, (número de consultas menor que 7, número de consultar maior ou igual a 7), variável qualitativa dicotômica;

d) **valor do Apgar no 5º minuto** (Apgar menor que 7, Apgar maior ou igual a 7), variável qualitativa dicotômica;

e) **presença de anomalia** (presença ou ausência), variável qualitativa dicotômica.

5.7 Análise estatística

O software estatístico utilizado foi o IBM SPSS Statistics versão 25.0 (IBM, Armonk – New York, EUA).

A análise descritiva foi composta pelo encontro das frequências absolutas e relativas, bem como pela construção de gráficos e tabelas.

A análise inferencial foi composta pela análise bivariada e multivariada. O *Odds Ratio* foi a medida de risco avaliada. Considerou-se estatisticamente significante um $p < 0.05$.

5.7.1 Escore de predição

O processo de seleção consistiu no uso das variáveis identificadas como fatores de risco para óbito neonatal, cujo *Odds Ratio* ajustado foi maior que 2.0, em uma revisão sistemática com meta-análise sobre mortalidade neonatal, a qual envolveu várias cidades brasileiras (VELOSO *et al*., 2019).

Para cada uma das variáveis foram atribuídas, de forma arbitrária, pontuações de acordo com a importância das variáveis no contexto do óbito neonatal. Deu-se três pontos para o peso < 2500 gramas, dois pontos para a presença de malformação congênita, dois pontos para a idade gestacional < 37 semanas, dois pontos para o Apgar < 7 no 5º minuto e um ponto para número de consultas pré-natais < 7 (Imagem 7). O ponto de corte, também escolhido de forma arbitrária, foi cinco pontos.

Imagem 1 - Distribuição do sistema de pontuação.

VARIÁVEL	PONTUAÇÃO
Peso < 2500 gramas	3
Presença de anomalia congênita	2
Idade gestacional < 37 semanas	2
APGAR < 7 no 5º minuto	2
Número de consultas pré-natais < 7	1

Fonte: elaborado pelos autores.

Calculou-se, a sensibilidade, especificidade, razão de probabilidade positiva (RPP), razão de probabilidade negativa (RPN), área sob a curva (AUC). Por fim, foi construída a curva ROC. O valor de *p* estatisticamente significativo adotado foi 0.05. Considerou-se como uma grande influência na probabilidade de ocorrência do óbito um RPP > 10 e um RPN < 0.1.

5.8. Aspectos éticos

5.8.1 Autorização

A Superintendência de Vigilância em Saúde (SUVISA) da Secretaria de Saúde do Estado de Alagoas (SESAU), número do processo 02000.0000025417/2020, autorizou os pesquisadores a coletarem os dados do Estado de Alagoas *in locu*, mediante concordância em não coletar os dados individuais dos participantes, a exemplo do nome da mãe, nome do pai e data de nascimento.

Por ser uma coleta de dados secundários, os quais podem ser encontrados via Departamento de Informática do Sistema Único de Saúde do Brasil (DATASUS), não houve a necessidade de submissão ao Comitê de Ética em Pesquisa (CEP/UFAL).

5.8.2 Riscos

Os participantes correram o risco de ter seus dados individuais divulgados ou estigmatizados por qualquer conteúdo revelado. Para minimizar esse risco, os pesquisadores criaram uma função no software desenvolvido pela equipe, a qual excluiu tais dados sigilosos. Além disso, os responsáveis pela SUVISA, os quais acompanharam os pesquisadores na coleta de dados, controlaram todo o processo, a fim de garantir o não-vazamento de dados do setor.

5.8.3 Benefícios

A população, por meio dos resultados deste estudo, conhecerá a realidade do Estado de Alagoas, bem como os fatores que mais apresentam risco ao óbito neonatal. Além disso, outro benefício, mais direcionado aos profissionais de saúde, é a proposta de uma escala de prevenção de óbito neonatal, auxiliando esses profissionais a preparar as gestantes e o ambiente de trabalho que atuam a receber um recém-nascido conforme classificado.

.

6 PRODUTO

1. **NEONATAL DEATH PREDICTION SCORE IN THE FIFTH MINUTE OF LIFE**, submetido segundo as normas da **PAEDIATRIC AND PERINATAL EPIDEMIOLOGY**.

6.1 Produto I

NEONATAL DEATH PREDICTION SCORE IN THE FIFTH MINUTE OF LIFE

NEONATAL DEATH PREDICTION SCORE

Felipe Camilo Santiago Veloso[1], Carine Ramos Accioly de Barros[1], Karin Melo Araújo[1], José Pedro Cassemiro Micheleto[1], Hellena Almeida Canuto[2], Miriã da Silva Moreira[2], Jorge Artur Peçanha de Miranda Coelho[2], Samir Buainain Kassar[1].

1 Faculty of Medicine, Federal University of Alagoas, Maceió, Alagoas, Brazil.

2 Interdisciplinary Group for Discovery of Knowledge in Large Volumes of Data (IGDKD), Federal University of Alagoas, Maceió, Alagoas, Brazil.

Corresponding Author: Prof. Dr. Samir Buainain Kassar. Faculdade de Medicina. Universidade Federal de Alagoas, Maceió, Alagoas, Brasil. Av. Lourival Melo Mota, S/N, Tabuleiro do Martins, Maceió, Alagoas, Brasil. CEP: 57.072-900.

SYNOPSIS

1 Research Question

What is the difference between a neonatal death prediction score constructed from Brazilian data and other neonatal death prediction scores?

2 What is already known?

The Clinical Risk Index for Babies (CRIB) had an AUC of 90%, the Score for Neonatal Acute Physiology (SNAP) an AUC of 87%. the Simplified Age-Weight and Sex mortality risk classification (SAWS) an AUC of 71% and the Neonatal Mortality Risk among neonates weighting 2000 g or less (NMR-2000) an AUC of 85.2%.

3 What does this study help?

Analyzing the database of one of the states of Brazil, the study allows us to understand the causal dynamics of neonatal deaths, in addition to proposing the elaboration of a neonatal death prediction score to be used by health professionals.

ABSTRACT E KEYWORDS

Context. The first week of life is the most critical for the newborn, especially in the first 24 hours of life. It is estimated that, annually, 2.7 million neonatal deaths occur worldwide, with 1 million of them occurring in the first week. In the literature, there are numerous proposals for prediction scores, whether for developed or developing countries, or for hospital or intensive care units.

Objective. Develop a neonatal death prediction score.

Methods. A case-control study that used public secondary data collected from the Live Births Information System (LBIS) and the Mortality Information System (MIS). The time span was five years (2016 – 2020). The two live births registered immediately after the occurrence of death (case) were considered control. The variables were gestational age, birth weight, number of prenatal consultations, APGAR at 5 minutes and congenital anomalies. The analyzes consisted of absolute and relative frequency, Crude Odds Ratio (COR) and Adjusted Odds Ratio (AOR). To construct the prediction score, the cutoff point, sensitivity, specificity, positive probability ratio (PPR), negative probability ratio (NPR) and area under the curve (AUC) were calculated.

Results. Weight < 2500 grams had an AOR of 7.56 (5.86, 9.74), the presence of malformation AOR 28.15 (16.73, 47.36), gestational age < 37 weeks AOR 6.06 (4.72, 7.78), the Apgar < 7 at the 5th minute AOR 61.61 (38.01, 99.88) and number of prenatal consultations < 7 AOR 1.29 (1.04, 1.59). The prediction score cutoff was five points, sensitivity 70.21%, specificity 96.65%, PPR 20.95, NPR 0.30 and AUC 0.896.

Conclusion. The prediction score is promising to predict neonatal death, showing a great influence on the probability when greater than five points, obtaining a better score when positive.

KEYWORDS – Neonatal mortality. Risk factors. Clinical Decision Rules.

MAIN TEXT

Context

Neonatal death consists of death between birth and the 27th day of life[1]. This period is commonly divided into early and late neonatal death, each with its causal particularities and epidemiological importance[2].

In the first period, between birth and the 7th day of life, avoidable causes are included, with prematurity, low birth weight and intrapartum complications being the most prevalent reasons[2,3]. In the second period, congenital anomalies are the most prevalent causes[3].

The first week of life is the most critical for the newborn, especially in the first 24 hours of life[4]. It is estimated that, annually, 2.7 million neonatal deaths occur worldwide, with 1 million of them occurring in the first week[3,4].

Therefore, it is important to use tools to help prevent these deaths, since they are mostly preventable causes[2,5,6]. In the literature, there are numerous proposals for prediction scores, whether for high, medium or low-income countries, or for hospital or intensive care units[5,7-9].

The purpose of this study is to develop a neonatal death prediction score in order to help health professionals understand and predict neonatal death.

Methods

A case-control study which used public secondary data collected from the Live Birth Information System (LBIS) and the Mortality Information System (MIS).

Neonatal deaths were considered cases and controls were the two live births recorded immediately after the death occurred. All neonatal deaths that occurred in the State of Alagoas (Brazil) between January 2016 and October 2020 were included, as well as the two live births recorded immediately after these neonatal deaths.

The primary variable was neonatal death. Secondary variables were gestational age, birth weight, prenatal consultations, Apgar at 5 minutes and congenital anomalies.

Data collection was performed using proprietary software developed in Python language version 3.8.8 (Python Software Foundation, Delaware, USA) and a pandas tabular data manipulation library version 1.2.3 (Python Software Foundation, Delaware, USA). Access to data consisted of performing a Linkage, that is, from the Birth Registration Number (BRN), the corresponding Death Registration Number (DRN) was found, as well as the two BRN subsequent to the time of death recorded in the DRN previously collected.

The statistical software used was IBM SPSS Statistics version 25.0 (IBM, Armonk – New York, USA). The descriptive analysis was composed by finding the absolute and relative frequencies, as well as the construction of graphs and tables. The inferential analysis consisted of bivariate and multivariate analysis. The Crude Odds Ratio (COR) and Adjusted Odds Ratio (AOR) were the measures of risk assessed. A $p < 0.05$ was considered statistically significant.

The process of elaborating the prediction score consisted of using the variables identified as risk factors for neonatal death, whose AOR was greater than 2.0, found in the study by Veloso et al (2019).

For each of the variables, scores were arbitrarily assigned according to the importance of the variables in the context of neonatal death. Three points were given for weight < 2500 grams, two points for the presence of congenital anomaly, two points for gestational age < 37 weeks, two points for Apgar < 7 points in the 5th minute and one point for the number of prenatal consultations < 7 times. The cut-off point was five points.

Sensitivity, Specificity, Positive Probability Ratio (PPR), Negative Probability Ratio (NPR), Area Under the Curve (AUC) were calculated and the ROC curve was constructed. A $p < 0.05$ was considered statistically significant. An PPR > 10

and an NPR < 0.1 were considered as a major influence on the probability of death.

Approval by the Research Ethics Committee was not necessary, as the data collected and used are in the public domain.

Results

Between 2016 and 2020, 6189 records were collected, of which 2089 were neonatal deaths. After applying the eligibility criteria, 5198 records remained, with 1138 deaths and 3860 live births (Image 1)

We found 1317 (25.3%) premature infants, 1180 (22.7%) low birth weight newborns, 677 (13%) with inadequate prenatal care, 555 (10.7%) with Apgar < 7 at the 5th minute and 229 (4.4%) with some congenital anomaly (Table 1).

Of the deaths, 931 (63.9%) newborns were low birth weight, 205 (15.3%) had some congenital anomaly, 957 (72.2%) were premature, 532 (40.5%) had Apgar < 7 at the 5th minute and 883 (68.2%) had inadequate prenatal care (Table 2).

Low birth weight was 33 times more likely to die (COR 33.17 [27.89,39.45]), the presence of congenital anomaly 28 times (COR 28.79 [18.77,44.18]), prematurity 25 times (COR 25.27 [21.49,29.71]), Apgar < 7 in the 5th minute 113 times (COR 113.49 [74.23,173.50]) and inadequate prenatal care 3 times (COR 3.65 [3.18,4.18]) (Table 2).

When adjusting the variables, low birth weight was 7 times more likely to die (AOR 7.56 [5.86,9.74]), the presence of congenital anomaly 28 times (AOR 28.15 [16.73,47.36]), prematurity 6 times (AOR 6.06 [4.72,7.78]), Apgar < 7 in the 5th minute 61 times (AOR 61.61 [38.01,99.88]) and inadequate prenatal care 1 time (AOR 1.29 [1.04,1.59]) (Table 2).

In the elaboration of the prediction score, sensitivity of 70.21%, specificity of 96.65%, PPR of 20.95, NPR of 0.30 and AUC 0.896 (0.883, 0.908) were found (Table 3; Image 2).

Comments

The study showed that 72.2% of deaths recorded between 2016 and 2020 in Alagoas were premature newborns, 68.2% had inadequate prenatal care, 63.9% were underweight, 40.5% had Apgar < 7 in the 5th minute and 15.3% had some congenital anomaly.

In addition, it was evidenced that Apgar < 7 in the 5th minute was 61 times more likely to die, followed by the presence of congenital anomaly with 28 times, low birth weight with 7 times, prematurity with 6 times and inadequate prenatal care with a turn.

Lansky et al (2014), when analyzing the profile of neonatal deaths in Brazil, showed that 82% of registered deaths were related to low birth weight and 81.7% to prematurity. Kassar et al (2013), when identifying risk factors for neonatal mortality, also showed that the main cause of neonatal death was low birth weight, with 69.9% of deaths recorded. Such findings corroborate the findings in our study, which pointed to prematurity and low birth weight as one of the main causes.

Sleutjes et al (2018), analyzing the risk factors for neonatal mortality in the State of São Paulo (Brazil), showed that 76.7% of registered deaths were caused by prematurity, 75% by low birth weight and 75% by a Apgar < 7. On the other hand, Vallely et al (2021), using data from the Papua New Guinea Perinatal Problems Identification System to describe the causes and avoidable factors associated with early neonatal death, showed that 23% of registered deaths were caused by prematurity , corroborating the findings of our study.

Cnattingius et al (2020), when using the Swedish database to investigate the association between the risk of neonatal death, showed that, of the 1,986 deaths recorded, 71.65% corresponded to extreme prematurity. In addition, while being born with a gestational age of 30 weeks is 10.9 times more likely to die, a gestational age of 22 weeks is 641.9 times more likely to die. On the other hand, Veloso et al (2019), when analyzing the risk of neonatal death in Brazil, showed

that the gestational age of 37 weeks or less is 5.74 times more likely to die, a number close to the finding in our study. Sleutjes et al (2018) pointed out that a gestational age less than 38 weeks has a 168 times greater chance of death.

Andegiorgish et al (2020), evaluating neonatal mortality and associated factors in Asmara (Eritrea), showed that being born with a gestational age of less than 37 weeks is 1.46 times more likely to die. On the other hand, Demitto et al (2016), when identifying the factors associated with neonatal mortality, pointed out that being premature at 28 weeks or less is 682.47 times more likely to progress to death.

Garcia et al (2017), analyzing the risk factors for neonatal mortality in Santa Catarina (Brazil), showed that an Apgar score < 7 in the 5th minute has a 19.08 times greater chance of death and low birth weight has a chance of 9.46 times of progressing to death. Lona Reys et al (2018), in turn, when evaluating the factors associated with neonatal mortality in Guadalajara (Mexico), pointed out that Apgar < 7 in the 5th minute has a 9.40 times greater chance of death, while low birth weight 6.30 times. Weddih et al (2019), when evaluating the factors associated with neonatal death in Nuaquexote (Mauritania), showed that a low birth weight newborn is 3.91 times more likely to die. Such findings showed the importance of Apgar in the risk of neonatal death, corroborating the findings of our study.

The study, when elaborating the prediction score, found sensitivity of 70.21%, specificity of 96.65%, PPR of 20.95, NPR of 0.30 and AUC of 89.6%. The International Neonatal Network (1993) published the Clinical Risk Index for Babies (CRIB) and, using six parameters and a result in the first 12 hours, found an AUC of 90%. In contrast, using 28 items to be collected in the first 24 hours of life, Richardson et al (1993) developed the Score for Neonatal Acute Physiology (SNAP), with an AUC of 87%. Our study, using five parameters, found an AUC of 89.6%, proving to be an alternative to be considered.

Rosenberg et al (2008) developed the Simplified Age-Weight and Sex mortality risk classification (SAWS) and, using the variables sex, gestational age and birth

weight, found an AUC of 71%. Also using three parameters collected in the first 24 hours, Medvedev et al (2020) developed the Neonatal Mortality Risk among neonates weighting 2000 g or less (NMR-2000), reaching an AUC of 85.2%. The scale proposed by this study proved to be superior to the proposals presented above, with an AUC of 89.6%.

It should be noted that our study used secondary data to develop a neonatal death prediction score. Szwarcwald et al (2019), when analyzing the quality of the data recorded in the Live Birth Information System (LBIS), showed agreement in all the variables tested, with the most fragile variable being the gestational age with a kappa value of 0.461, evidencing a quality of the data that make up the analyzed database.

Finally, a point to be highlighted is the great positive influence that our score has when the score is greater than 5 (PPR > 10), showing a high probability of death. On the other hand, the same cannot be said when the score is less than 5 (NPR > 0.1).

Conclusion

The prediction score is promising to predict neonatal death, showing a great influence on the probability when greater than five points, obtaining a better score when positive.

REFERENCES

[1] Pathirana J, Muñoz FM, Abbing-Karahagopian V, Bhat N, Harris T, Kapoor A et al. Neonatal death: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2016; 34:6027-2037.

[2] Veloso FCS, Kassar LML, Oliveira MJC, de Lima THB, Bueno NB, Gurgel RQ et al. Analysis of neonatal mortality risk factors in Brazil: a systematic review and meta-analysis of observational studies. J Pediatr (Rio J) 2019; 95:519-530.

[3] Vallely LM, Smith R, Laman M, Riddell MA, Mengi A, Au L et al. Early neonatal death review from two provinces in Papua New Guinea: A retrospective analysis. J Paediatr Child Health 2021; 57:841-846.

[4] Lehtonen L, Gimeno A, Parra-Llorca A, Vento M. Early neonatal death: A challenge worldwide. Semin Fetal Neonatal Med 2017; 22:153-160.

[5] Dorling JS, Field DJ, Manktelow B. Neonatal disease severity scoring system. Arch Dis Child Fetal Neonatal Ed 2005; 90:F11-F16.

[6] Pedrosa LDCO, Sarinho SW, Ordonha MR. Quality of information analysis on basic causes of neonatal deaths recorded in the Mortality Information System: a study in Maceió, Alagoas State, Brazil, 2001-2002. Cad Saude Publica 2007; 23:2385-2395.

[7] International Neonatal Network. The CRIB (Clinical Risk Index for Babies) Score: a tool for assessing initial neonatal risk and comparing performance of neonatal intensive-care units. Lancet 1993; 342:193-198.

[8] Rosenberg RE, Ahmed S, Saha SK, Ahmed NU, Chowdhury A, Law PA et al. Simplified Age-Weight Mortality Risk Classification for Very Low Birth Weight Infants in Low-Resource Settings. J Pediatr 2008; 153:519-524.

[9] Medvedev MM, Brotherton H, Gai A, Tann C, Gale C, Waiswa P et al. Development and validation of a simplified score to predict neonatal mortality risk among neonates weighing 2000 g or less (NMR-2000): an analysis using data from the UK and The Gambia. Lancet Child Adolesc Health 2020; 4:299-311.

[10] Lansky S, Friche AAL, da Silva AAM, Campos D, Bittencourt DAS, de Carvalho ML et al. Birth in Brazil survey: neonatal mortality, pregnancy and childbirth quality of care. Cad Saude Publica 2014; 30:S1-S15.

[11] Kassar SB, Melo AMC, Coutinho SB, Lima MC, Lira PIC. Determinants of neonatal death with emphasis on health care during pregnancy, childbirth and reproductive history. J Pediatr (Rio J) 2013; 89:269-277.

[12] Sleutjes FCM, Parada CMGL, Carvalhaes MABL, Temer MJ. Risk factors for neonatal death in na inland region in the State of São Paulo Brazil. Cien Saude Colet 2018; 23:2713-2720.

[13] Cnattingius S, Johansson S, Razaz N. Apgar Score and Risk of Neonatal Death among Preterm Infants. N Engl J Med 2020; 383:49-57.

[14] Andegiorgish AM, Andemariam M, Temesghen S, Ogbai L, Ogbe Z, Zeng L. Neonatal mortality and associated factors in the specialized neonatal care unit Asmara, Eritrea. BMC Public Health 2020; 20: 10.

[15] Demitto MO, Gravena AAF, Dell'Agnolo CM, Antunes MB, Pelloso SM. High risk pregnancies and factors associated with neonatal death. Rev Esc Enferm USP 2017; 51:e03208.

[16] Garcia LP, Fernandes CM, Traebert J. Risk factors for neonatal death in the capital city with the lowest infant mortality rate in Brazil. J Pediatr (Rio J) 2019; 95:194-200.

[17] Lona Reyes JC, Ramírez ROP, Ramos LL, Ruiz LMG, Vázquez EAB, Patino VR. Neonatal mortality and associated factors in newborn infants admitted to a Neonatal Care Unit. Arch Argent Pediatr 2018; 116:42-48.

[18] Weddih A, Ahmed MLCB, Sidatt M, Abdelghader N, Abdelghader F, Ahmed A et al. Prevalence and factors associated with neonatal mortality among neonates hospitalized at the National Hospital Nouakchott, Mauritania. Pan Afr Med J 2019; 34:152.

[19] Richardson DK, Gray JE, McCormick MC, Workman-Daniels K, Goldmann DA. Score for Neonatal Acute Physiology: a physiologic severity index for neonatal intensive care. Pediatrics 1993; 91:617-623.

[20] Szwarcwald CL, Leal MC, Esteves-Pereira AP, de Almeida WS, de Frias PG, Damacena GN et al. Evaluation of data from the Brazilian Information System on Live Births (SINASC). Cad Saude Publica 2019; 35:e00214918.

FIGURE LEGENDS

Image 1. Data selection flowchart.

Image 2. ROC curve.

TABLES

Table 1. Descriptive analysis of the data.

		5198 records	
Gestational age	≥ 37 weeks	3867	74.4%
	< 37 weeks	1317	25.3%
	Ignored	14	0.3%
Birth weight	≥ 2500 grams	4018	77.3%
	< 2500 grams	1180	22.7%
Number of prenatal consultations	None	105	2%
	1 a 3	572	11%
	4 a 6	1627	31.3%
	≥ 7	2837	54.6%
	Ignored	57	1.1%
APGAR in the 5th minute	≥ 7	4619	88.9%
	< 7	555	10.7%
	Ignored	24	0.5%
Congenital anomalies	Presence	229	4.4%
	Absence	4953	95.3%
	Ignored	16	0.3%

Table 2. Bivariate and multivariate analysis.

	Death		COR (95% IC)	AOR (95% IC)
	Yes	No		
Weight				
< 2500 grams	931 (69.60%)	249 (6.50%)	33.17 (27.89 – 39.45)	7.56 (5.86 – 9.74)
≥ 2500 grams	407 (30.40%)	3611 (93.50%)		
Congenital anomalies				
Yes	205 (15.32%)	24 (0.63%)	28.79 (18.77 – 44.18)	28.15 (16.73 – 47.36)
No	1133 (84.68%)	3820 (99.37%)		
Gestational age				
< 37 weeks	957 (72.20%)	360 (9.30%)	25.27 (21.49 – 29.71)	6.06 (4.72 – 7.78)
≥ 37 weeks	368 (27.80%)	3499 (90.70%)		
APGAR in the 5th minute				
< 7	532 (40.50%)	231 (0.60%)	113.49 (74.23 – 173.50)	61.61 (38.01 – 99.88)
≥ 7	782 (59.50%)	3837 (99.40%)		
Prenatal				
< 7 consultations	883 (68.20%)	1421 (36.90%)	3.65 (3.18 – 4.18)	1.29 (1.04 – 1.59)
≥ 7 consultations	412 (31.80%)	2425 (63.10%)		

Table 3. Sensitivity, specificity, positive probability ratio, negative probability ratio and area under the curve.

	DEATH	
	YES	NO
Score ≥ 5	884	128
Score < 5	375	3701
Sensitivity	70.21%	
Specificity	96.65%	
Positive Probability Ratio	20.95	
Negative Probability Ratio	0.30	
Area under the curve.	0.896	

FIGURES

Image 1. Data selection flowchart.

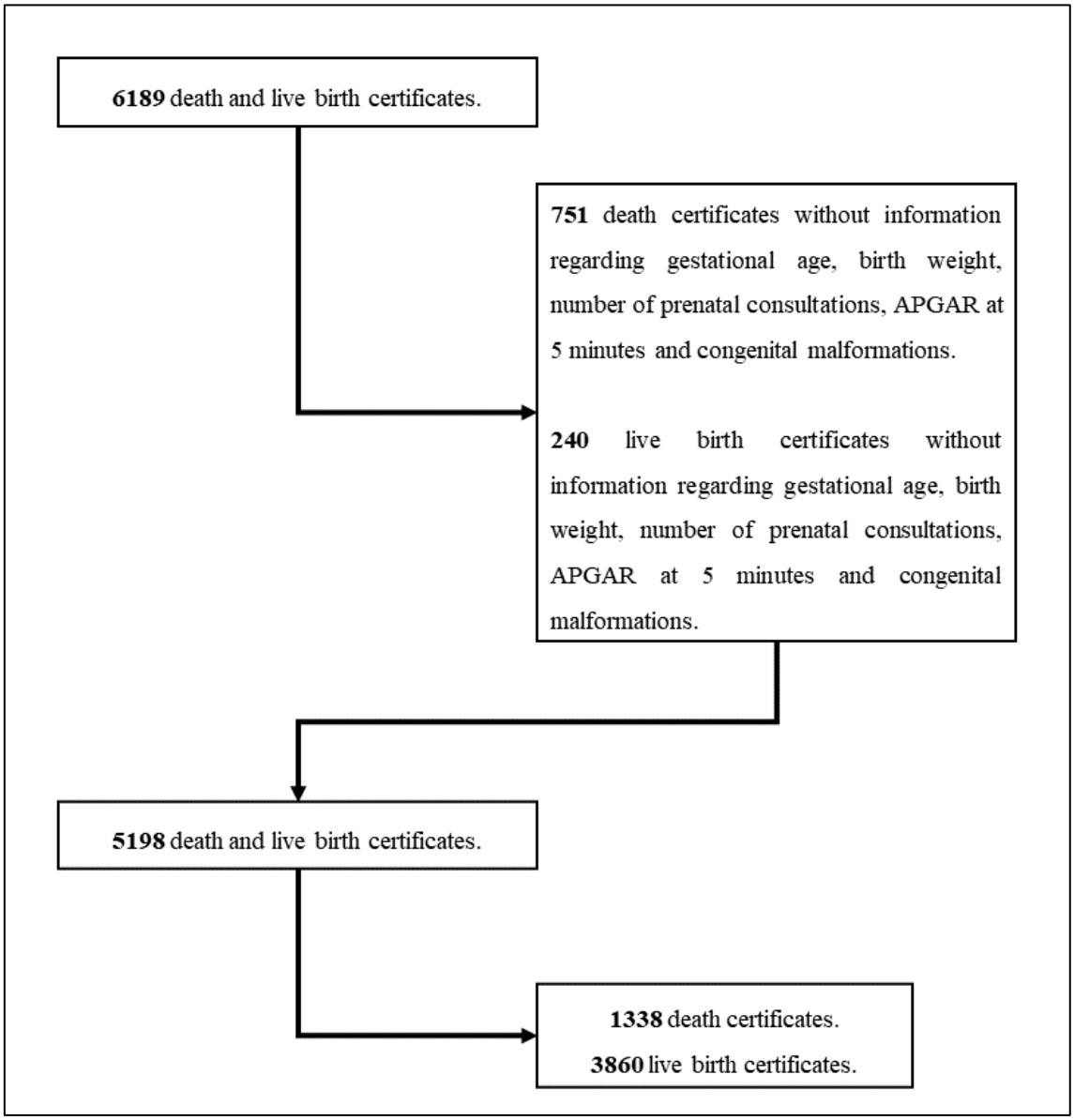
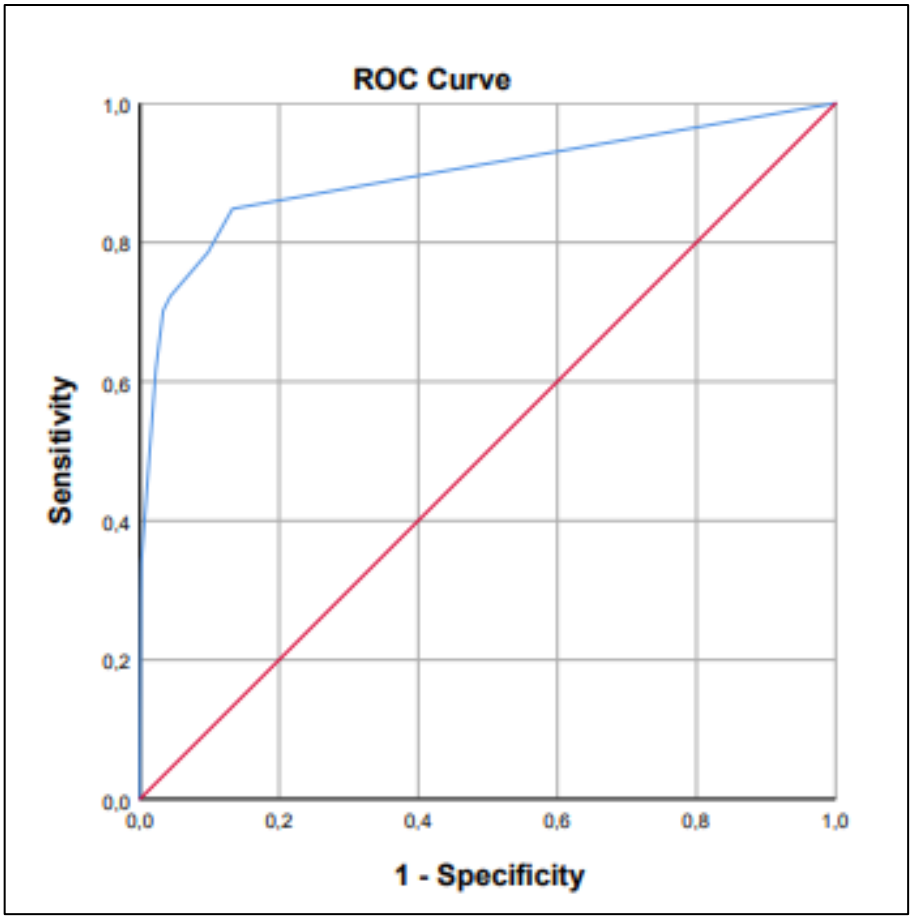


Image 2. ROC curve.



7 CONCLUSÕES

O estudo mostrou que 72.2% dos óbitos registrados entre 2016 e 2020 em Alagoas eram recém-nascidos prematuros, 68.2% apresentaram pré-natal inadequado, 63.9% eram de baixo peso, 40.5% apresentaram Apgar < 7 no 5º minuto e 15.3% possuíam alguma anomalia congênita. Além disso, o Apgar < 7 no 5º minuto apresentou 61 vezes mais chance de óbito, seguido da presença de anomalia congênita com 28 vezes, baixo peso ao nascer com 7 vezes, prematuridade com 6 vezes e pré-natal inadequado com uma vez.

O escore de predição proposto obteve uma sensibilidade de 70.21%, especificidade de 96.65%, RPP de 20.95, RPN de 0.30 e AUC de 89.6%. Diante disso, tal escore mostra-se promissor para predizer o óbito neonatal, apresentando uma grande influência na probabilidade de ocorrência de óbito neonatal quando maior que cinco pontos.

8 LIMITAÇÕES E PERSPECTIVAS

A nossa proposta de escore utilizou dados secundários, o que pode levantar uma desconfiança dos dados. SZWARCWALD *et al* (2019) publicaram um estudo analisando a qualidade dos dados registrados no Sistema de Informações sobre Nascidos Vivos (SINASC), uma das bases utilizadas em nosso estudo e que está presente juntamente com o Sistema de Informações sobre Mortalidade (SIM) no Departamento de Informática do Sistema Único de Saúde do Brasil (DATASUS). Tal estudo mostrou que houve concordância em todas as variáveis testadas, sendo a variável de maior fragilidade a idade gestacional com valor de *kappa* de 0.461, evidenciando a boa qualidade dos dados que compõem o SINASC (SZWARCKWALD *et al*., 2019).

Por fim, um ponto a ser destacado é a grande influência que o escore proposto possui quando a pontuação é maior que 5, pois o RPP foi maior que 10. Isso mostra que há uma probabilidade alta de que o recém-nascido irá evoluir para o óbito. Em contrapartida, o mesmo não pode ser dito quando o escore proposto for menor que 5, pois o RPN foi maior que 0.3, mostrando que há uma pequena influência na probabilidade.

O escore de predição proposto é um dispositivo de rápido e fácil acesso, podendo ser construído em 5 minutos. Por isso, a intenção dessa proposta é difundir esse escore, principalmente nos países de média e baixa renda, onde os sistemas de saúde são deficientes em vários aspectos. Sendo um escore construído a partir de dados do Brasil, onde o perfil causal é semelhante a outros países de média e baixa renda, o escore proposto mostra-se promissor e uma opção interessante a ser utilizada em estudos prospectivos no contexto da mortalidade neonatal.

REFERÊNCIAS

BELUZO, C. E. Towards neonatal mortality risk classification: A data-driven approach using neonatal, maternal, and social factors. Informatics in Medicine Unlocked, v.20, 100398, 2020. DOI: < doi.org/10.1016/j.imu.2020.100398 >. Disponível em: < https://www.sciencedirect.com/science/article/pii/S2352914820302112 >. Acesso em 06 fev. 2022.

BRASIL. Ministério da Saúde. DATASUS: Informações de Saúde (TABNET). Mortalidade – 1996 a 2019, pela CID – 10. Óbitos neonatais entre 1999 e 2019. Brasília, 2021. Disponível em: < http://www2.datasus.gov.br/DATASUS/index.php?area=0205&id=6937&VObj=http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sim/cnv/obt10 >. Acesso em 06 fev. 2022.

BRASIL. Ministério da Saúde. DATASUS: Informações de Saúde (TABNET). Mortalidade – 1996 a 2019, pela CID – 10. Óbitos neonatais em Alagoas entre 1999 e 2019. Brasília, 2021. Disponível em: < http://www2.datasus.gov.br/DATASUS/index.php?area=0205&id=6937&VObj=http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sim/cnv/obt10 >. Acesso em 06 fev. 2022.

BRASIL. Ministério da Saúde. DATASUS: Informações de Saúde (TABNET). Mortalidade – 1996 a 2019, pela CID – 10. Óbitos neonatais no Nordeste do Brasil entre 1999 e 2019. Brasília, 2021. Disponível em: < http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sim/cnv/inf10uf.def Acesso em 06 fev. 2022.

CNATTINGIUS, S. Apgar Score and Risk of Neonatal Death among Preterm Infants. The New England journal of medicine, v.383, n.1, p.49-57, 2020. DOI: < doi.org/ 10.1056/NEJMoa1915075 >. Disponível em: < https://pubmed.ncbi.nlm.nih.gov/32609981/ >. Acesso em 06 fev. 2022.

DORLING, J. S.; FIELD, D. J.; MANKTELOW, B. Neonatal disease severity scoring system. Archives of disease in childhood. Fetal and neonatal edition, v.90, n.1, F11-F16,

2005. DOI: < doi.org/10.1136/adc.2003.048488 >. Disponível em: < https://pubmed.ncbi.nlm.nih.gov/15613564/ >. Acesso em 06 fev. 2022.

INTERNATIONAL NEONATAL NETWORK. The CRIB (Clinical Risk Index for Babies) Score: a tool for assessing initial neonatal risk and comparing performance of neonatal intensive-care units. Lancet, v.342, n.8865, p.193-198, 1993. Disponível em: < https://pubmed.ncbi.nlm.nih.gov/8100927/ >. Acesso em 06 fev. 2022.

KASSAR, S. B. et al. Determinants of neonatal death with emphasis on health care during pregnancy, childbirth and reproductive history. Jornal de Pediatria, v.89, n.3, p.269-277, 2013. DOI: < doi.org/ 10.1016/j.jped.2012.11.005 >. Disponível em: < https://pubmed.ncbi.nlm.nih.gov/23680300/ >. Acesso em 06 fev. 2022.

LANSKY, S. et al. Birth in Brazil survey: neonatal mortality, pregnancy and childbirth quality of care. Caderno de Saúde Pública, v.30, suppl.1, S1-S15, 2014. DOI: < doi.org/10.1590/0102-311X00133213 >. Disponível em: < https://www.scielosp.org/article/csp/2014.v30suppl1/S192-S207/ >. Acesso em 06 fev. 2022.

LEHTONEN, L. Early neonatal death: A challenge worldwide. Seminars in fetal & neonatal medicine, v.22, n.3, p.153-160, 2017. DOI: < doi.org/ 10.1016/j.siny.2017.02.006 >. Disponível em: < https://pubmed.ncbi.nlm.nih.gov/28238633/ >. Acesso em 06 fev. 2022.

LIMA, S. S. et al. Assessment of the impact of prenatal, childbirth, and neonatal care on avoidable neonatal deaths in Pernambuco State, Brazil: an adequacy study. Caderno de Saúde Pública, v.36, n.2, e.00039719, 2020. DOI: < doi.org/10.1590/0102-311X00039719 >. Disponível em: < https://www.scielo.br/j/csp/a/xjBngQW39sVHzVBL4q9Zj3P/?lang=pt >. Acesso em 06 fev. 2022.

MÁRQUEZ-GONZÁLEZ, H. et al. Development and validation of the Neonatal Mortality Score-9 Mexico to predict mortality in critically ill neonates. Archivos argentinos de pediatria, v.113, n.3, p.213-220, 2015. DOI: < doi.org/10.5546/aap.2015.213 >. Disponível em: < https://pubmed.ncbi.nlm.nih.gov/25996319/ >. Acesso em 12 abr. 2022.

MARSHALL, G. et al. A new score for predicting neonatal very low birth weight mortality risk in the NEOCOSUR South American Network. Journal of Perinatology, v.25, n.9, p.577-582, 2005. DOI: < doi.org/10.1038/sj.jp.7211362 >. Disponível em: < https://pubmed.ncbi.nlm.nih.gov/16049510/ >. Acesso em 12 abr. 2022.

MCLEOD, J. S. et al. Comparing mortality risk models in VLBW and preterm infants: systematic review and meta-analysis. Journal of Perinatology, v.40, n.5, p.695-703, 2020. DOI: < doi.org/10.1038/s41372-020-0650-0 >. Disponível em: < https://pubmed.ncbi.nlm.nih.gov/32203174/ >. Acesso em 12 abr. 2022.

MEDIRATTA, R. P. et al. Derivation and validation of a prognostic score for neonatal mortality in Ehiopia: a case-control study. BMC Pediatrics, v.20, n.1, p.238, 2020. DOI: < doi.org/10.1186/s12887-020-02107-8 >. Disponível em: < https://pubmed.ncbi.nlm.nih.gov/32434513/ >. Acesso em 12 abr. 2022.

MEDVEDEV, M. M. et al. Development and validation of a simplified score to predict neonatal mortality risk among neonates weighing 2000 g or less (NMR-2000): an analysis using data from the UK and The Gambia. The Lancet. Child & adolescent health, v.4, n.4, p.299-311, 2020. DOI: < doi.org/10.1016/ S2352-4642(20)30021-3 >. Disponível em: < https://pubmed.ncbi.nlm.nih.gov/32119841/ >. Acesso em 06 fev. 2022.

PARRY, G. et al. CRIB II: an update of the clinical risk index for babies score. Lancet, v.361, n.9371, p.1789-1791, 2003. DOI: < doi.org/ 10.1016/S0140-6736(03)13397-1 >. Disponível em: < https://pubmed.ncbi.nlm.nih.gov/12781540/ >. Acesso em: 09 ago. 2021.

PATHIRANA, J. et al. Neonatal death: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine, v.34, n.49, p.6027-6037, 2016. DOI: < doi.org/10.1016/j.vaccine.2016.03.040 >. Disponível em: < https://pubmed.ncbi.nlm.nih.gov/27449077/ >. Acesso em 06 fev. 2022.

PEDROSA, L. D. C. O. et al. Quality of information analysis on basic causes of neonatal deaths recorded in the Mortality Information System: a study in Maceió, Alagoas State,

Brazil, 2001-2002. Caderno de Saúde Pública, v.23, n.10, p.2385-2395, 2007. DOI: < doi.org/10.1590/S0102-311X2007001000013 >. Disponível em: < https://www.scielo.br/j/csp/a/gMQdS6sFkLQ7Sh7kMjX6dXb/?lang=pt >. Acesso em 06 fev. 2022.

RICHARDSON, D. K. et al. Birth weight and illness severity: independent predictors of neonatal mortality. Pediatrics, v.91, n.5, p.969-975, 1993. Disponível em: < https://pubmed.ncbi.nlm.nih.gov/8474818/ >. Acesso em: 09 ago. 2021.

RICHARDSON, D. K. et al. Score for Neonatal Acute Physiology: a physiologic severity index for neonatal intensive care. Pediatrics, v.91, n.3, p.617-623, 1993. Disponível em: < https://pubmed.ncbi.nlm.nih.gov/8441569/ >. Acesso em: 09 ago. 2021.

RICHARDSON, D. K. et al. SNAP-II and SNAPPE-II: Simplified newborn illness severity and mortality risk scores. The Journal of Pediatrics, v.138, n.1, p.92-100, 2001. DOI: < doi.org/ 10.1067/mpd.2001.109608 >. Disponível em: < https://pubmed.ncbi.nlm.nih.gov/11148519/ >. Acesso em: 09 ago. 2021.

ROSENBERG, R. E. et al. Simplified Age-Weight Mortality Risk Classification for Very Low Birth Weight Infants in Low-Resource Settings. The Journal of Pediatrics, v.153, n.4, p.519-524, 2008. DOI: < doi.org/10.1016/j.jpeds.2008.04.051 >. Disponível em: < https://www.sciencedirect.com/science/article/abs/pii/S0022347608003120 >. Acesso em 06 fev. 2022.

SZWARCWALD, C. L. et al. Evaluation of data from the Brazilian Information System on Live Births (SINASC). Cadernos de Saúde Pública, v.35, n.10, e00214918, 2019. DOI: < doi.org/10.1590/0102-311X00214918 >. Disponível em: < https://www.scielo.br/j/csp/a/dqy9gbh3k8fJBjYHVBwbMnS/abstract/?lang=pt >. Acesso em 06 fev. 2022.

United Nations Internacional Children's Emergency Fund – UNICEF. Neonatal Mortality. Nova Iorque (EUA), 2020. Disponível em: < https://data.unicef.org/topic/child-survival/neonatal-mortality/ >. Acesso em 06 fev. 2022.

VALLELY, L. M. et al. Early neonatal death review from two provinces in Papua New Guinea: A retrospective analysis. Journal of paediatrics and child health, v.57, n.6: p.841-846, 2021. DOI: < doi.org/ 10.1111/jpc.15333 >. Disponível em: < https://pubmed.ncbi.nlm.nih.gov/33450113/ >. Acesso em 06 fev. 2022.

VELOSO, F. C. S. et al. Analysis of neonatal mortality risk factors in Brazil: a systematic review and meta-analysis of observational studies. Jornal de Pediatria, v.95, n.5, p.519-530, 2019. DOI: < doi.org/10.1016/j.jped.2018.12.014 >. Disponível em: < https://www.scielo.br/j/jped/a/wZS4WFQPR8j9qrgk9NBrhnq/?lang=en >. Acesso em 06 fev. 2022.

APÊNDICE

UNIVERSIDADE FEDERAL DE ALAGOAS
FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS
MESTRADO ACADÊMICO

Maceió – AL, 15 de dezembro de 2020.

À Secretaria de Estado da Saúde – SESAU
A/C: Superintendência de Vigilância em Saúde – SUVISA
Prezado Senhor Herbert Charles Silva Barros

Solicito a Vossa Senhoria autorização para que os alunos Felipe Camilo Santiago Veloso (Programa de Pós-Graduação em Ciências Médicas – Mestrado Acadêmico – da Universidade Federal de Alagoas), Carine Ramos Accioly de Barros (Curso de Graduação em Medicina da Universidade Federal de Alagoas) e Hellena Almeida Canuto (Curso de Graduação em Ciências da Computação da Universidade Federal de Alagoas) possam realizar pesquisa de coleta de dados necessários para a realização da submissão do projeto de pesquisa intitulado "Construção de uma Escala de Predição de Óbito Neonatal" em revistas científicas. Orientador: Prof. Dr. Samir Buanain Kassar.

Os objetivos deste estudo são:

1 Elaborar uma escala de predição de morte neonatal.

2 Traçar um perfil epidemiológico dos óbitos neonatais no Estado de Alagoas entre os anos de 2016 e 2020.

3 Indicar os fatores de risco e proteção ao óbito neonatal no Estado de Alagoas entre os anos de 2016 e 2020.

Os dados necessários são:

1 Coletar as variáveis dos dados epidemiológicos da Declaração de Nascido-Vivo: Estado de ocorrência; Município do nascimento; Local do nascimento; Idade da mãe; estado civil da mãe; escolaridade da mãe; ocupação da mãe; Número de filhos vivos; Número de filhos mortos; Estado de residência; Município de residência; Tipo de gravidez; Semanas de gestação; Tipo de parto; Números de consultas de pré-natal; data de nascimento; hora do nascimento; sexo; Apgar 1º minuto; Apagar 5º minuto; Raça/Cor; Peso ao nascer; Anomalia; Número de gestações anteriores.

2 Coletar as variáveis dos dados epidemiológicos da Declaração de Óbito: Data do óbito; Hora do óbito; Data do nascimento; Idade; Sexo; Raça/Cor; Estado de residência; Município de residência; Local da ocorrência do óbito; Estado do óbito; Município do óbito; Idade da mãe; Escolaridade da mãe; Ocupação da mãe; Número de filhos vivos; Número de filhos mortos; Tipo de gravidez; Semanas de gestação; Tipo de parto; Peso ao nascer; Causas da morte Parte I; Causas da morte Parte II.

Certos de contarmos com a compreensão e colaboração de todos que fazem esta instituição, desde já ficamos agradecidos.

Sem mais para o momento, reforçamos nosso sentimento de apreço e estima.

Atenciosamente,

Prof. Dr. Samir Buanain Kassar

Orientador

ANEXO

ESTADO DE ALAGOAS
SECRETARIA DE ESTADO DA SAÚDE
SUPERINTENDÊNCIA DE VIGILÂNCIA EM SAÚDE
Avenida da Paz, 1068 – Jaraguá - Maceió - AL – CEP: 57022-050
Fone: (82) 3315-1110 CNPJ.: 12.200.259/0001-65

TERMO DE AUTORIZAÇÃO n° 003/2020

Declaramos, para fins de comprovação junto ao Comitê de Ética em Pesquisa, que autorizamos os pesquisadores Felipe Camilo Santiago Veloso (Programa de Pós Graduação em Ciência Médicas – Mestrado Acadêmico da Universidade Federal de Alagoas), Carine Ramos Accioly de Barros (Curso de Graduação em Medicina da Universidade Federal de Alagoas) e Hellena Almeida Canuto (Curso de Graduação em Ciências da Computação da Universidade Federal de Alagoas) sob a responsabilidade do Prof. Dr. Samir Buanain Kassar, a coletar dados pertinentes ao objetivo da pesquisa intitulada: **"Construção de uma Escala de Predição de óbito Neonatal"**.

Maceió, 23 de dezembro de 2020.

HERBERT CHARLES SILVA BARROS
Superintendente de Vigilância em Saúde

ALAGOAS

Termo (5484281) SEI E:02000.0000025417/2020 / pg. 1

PAEDIATRIC AND PERINATAL EPIDEMIOLOGY

Author Guidelines

Contents

1. SUBMISSION

Authors should kindly note that submission implies that the content has not been published or submitted for publication elsewhere except as a brief abstract in the proceedings of a scienti c meeting or symposium.

Once the submission materials have been prepared in accordance with the Author Guidelines, manuscripts should be submitted online at https://mc.manuscriptcentral.com/ppe Click here for more details on how to use ScholarOne.

Data protection:

By submitting a manuscript to or reviewing for this publication, your name, email address, and a liation, and other contact details the publication might require, will be used for the regular operations of the publication, including, when necessary, sharing with the publisher (Wiley) and partners for production and publication. The publication and the publisher recognise the importance of protecting the personal information collected from users in the operation of these services, and have practices in place to ensure that steps are taken to maintain the security, integrity, and privacy of the personal data collected and processed. You can learn more at https://authorservices.wiley.com/statements/data-protectionpolicy.html.

Preprint Policy:

Please review Wiley's preprint policy here.

However, Wiley also knows that the use of preprint servers is not universally accepted and that individual journals and/or societies may approach submission of preprints differently. Please see below for the speci c policy language.

This journal will consider for reviews previously available as preprints on non-commercial servers such as ArXiv, bioRxiv, psyArXiv, SocArXiv, engrXiv, etc. Authors may also post the submitted version of a manuscript to non-commercial servers at any time. Authors are requested to update any pre-publication versions with a link to the nal published article.

Social Media Quote:

When submitting an Original article you will be asked to also include a social media information

- We will post the quote on both Twitter and Facebook.
- We require that you provide a Tweetable quote of 280 characters or less, (in the manuscript and at the submission online portal), summarising the main ndings of the paper.
- Identify a single gure or a small table in the manuscript that will be posted along with the quote on social media.
- If you have a Twitter or Facebook account, we request that you provide them so we may tag you. Please follow us on Twitter @PPE_Journal, and Facebook at Facebook at Paediatric and Perinatal Epidemiology.

For help with submissions, please contact: PPEoffice@wiley.com.

We look forward to your submission.

2. AIMS AND SCOPE

Paediatric and Perinatal Epidemiology welcomes original research, brief reports, reviews (including systematic reviews and meta-analysis), letters to the editor, and debates, as well as papers describing the methods of large epidemiological studies or novel cohort or longitudinal study designs. Topics of interest include the application of epidemiologic methods to studies of fertility, pregnancy and obstetrical complications, birth outcomes, child health and development, and the in uence of the foetal and early environment on child or adult health. We also encourage submissions on the development and applications of new and innovative methods.

All authors are expected to meet the International Committee of Medical Journal Editors Uniform Criteria for Authorship (http://www.icmje.org/), which they con rm by their signature on the letter of submission.

3. MANUSCRIPT CATEGORIES AND REQUIREMENTS

Editor's Note papers and Debate papers are by invite only. If you are invited, you should state your approval to submit by the Editor-in-chief in the cover letter.

Case Reports

The journal does not accept case reports. Authors of case reports are encouraged to submit to the Wiley Open Access journal, Clinical Case Reports (www.clinicalcasesjournal.com), which aims to directly improve health outcomes by identifying and disseminating examples of best clinical practice.

Manuscript submission

Paediatric and Perinatal Epidemiology requires all manuscripts to be submitted electronically at https://mc.manuscriptcentral.com/ppe. Login or click the “Create Account” option if you are a rst-time user of the ScholarOne system. Full instructions and support for authors(and reviewers) are available on the site. Support can be contacted by email at support@scholarone.com or at
http://authorservices.wiley.com/bauthor/journal.asp. If you have trouble submitting online, PPE’s Editorial Assistant (PPEoffice@wiley.com) will be able to assist.

Word and references limits

Except where noted below, all manuscripts are to include a structured abstract and uniform section and subsection headings. The structured abstract (no more than 300 words) should include the following: Background, Objectives, Methods, Results, and Conclusions.

- Original articles: Submissions may not exceed 3500 words, with a maximum of 6 tables and gures combined, and up to 60 references. They should include a structured abstract (no more than 300 words; see “original submission” format below).
- Systematic review and meta-analysis articles: Submissions may not exceed 4500 words, with a maximum of 8 tables and gures combined and up to 75 references. They should include a
- structured abstract (no more than 300 words; see “Systematic reviews and meta-analysis” format below).

- Research protocol: Submissions should not exceed 4500 words, with a maximum of 8 tables and gures combined and up to 60 references. They should include a structured abstract (no more than 300 words; see “Study Design” format below).
- Methodology: Submissions should not exceed 3500 words, with a maximum of 6 tables and gures combined and up to 60 references. They should include a structured abstract (no more than 300 words; see “original submission” format below).
- Brief report: Submissions should not exceed 1500 words, with a maximum of 3 tables and gures combined, and up to 30 references. They should include a structured abstract (no more than 300 words; see “Original submission” format below).
- Debate: Submissions should not exceed 1500 words with a maximum of 1 table or gure and no more than 10 references. The title should be in the following format: e.g. “Point: The value of descriptive series analysis: The case of Portugal” or “Counterpoint: The value of descriptive series analysis: The case of Portugal”. An abstract is not required.
- Letters to the editor: Submissions should not exceed 500 words with a maximum of 6 references, including the original manuscript to which the letter is responding. An abstract is not required.

4. PREPARING YOUR SUBMISSION

General style conventions and formatting requirements

All manuscripts should be submitted in English using United Kingdom spelling and grammar conventions. Manuscripts should be typed with double spacing in Calibri font, 12 points. Pages should be numbered consecutively in the bottom centre. Do not fully justify the text.

Style conventions

In an e ort to standardise language use throughout the journal, Paediatric and Perinatal Epidemiology has adopted the following style conventions:

- Birthweight not birth weight; stillbirth not still birth.
- Breast feeding (noun) not breastfeeding; and breast-feeding mothers (adjective).
- Preterm or low birthweight never premature.
- Confidence intervals; not confidence limits.
- Multivariable not multivariate, for regression models with a single outcome variable.
- Parity to refer to the number of prior livebirth or stillbirth delivered at ≥20 weeks. Use parity zero if the pregnant or delivering woman has had no previous livebirths

or stillbirths and refer to her as a primipara (plural primiparae). A woman who has had at least one prior viable pregnancy is a multipara (plural multiparae).

Parts of the Manuscript

The manuscript should be submitted in separate les: main text le; gures.

Main Text File

The text le should be presented in the following order:

i. A short informative title containing the major key words. The title should not contain abbreviations

(see Wiley's best practice SEO tips); ii. A short running title of less than 40 characters;

iii. The full names of the authors; iv. The author's institutional a liations where the work was conducted, with a footnote for the author's present address if di erent from where the work was conducted; v. Abstract and keywords;

vi. Main text;

vii. Acknowledgments;

viii. References;

ix. Tables (each table complete with title and footnotes);

x. Figure legends;

xi. Appendices (if relevant).

Figures and supporting information should be supplied as separate les.

Body of text

- Do NOT indent paragraphs. Instead separate paragraphs with a blank extra line between paragraphs.
- Con dence intervals should be put in round brackets, separated by a comma (not a dash). For example, RR 2.31, 95% CI 1.90, 2.74; or RR 2.31 (95% CI 1.90, 2.74).
- Do not insert line numbers in the document.
- Ethics/human subjects statement (e.g, institutional review board approval) is required; it should be included as the last sentence of the rst paragraph under Methods.

Reporting of numerical data

- Report percentages and risks with one digit, and risk estimates and CIs to two significant digits. Round accordingly, reporting numbers appearing more than once consistently.

- Confidence intervals should be put in round brackets, separated by a comma (see example above).

P-values and con dence intervals

- We strongly discourage the use of P-values or statements that re ect “statistical significance” testing. The use of P-values is permitted for the following three scenarios only: (a) tests for linear and non-linear trends; (b) tests of interactions; and (c) multiple degrees of freedom tests (e.g, ANOVA).
- All ratio (OR, RR, HR) and di erence measures should be accompanied by a 95% con dence interval.

Title page

- Title: Be concise; declaring the type of study design is encouraged; do not specify the study (sample) size.
- List of authors (do not list quali cations or academic titles), with full names, each followed by a superscript number (not letter) to link with the institution at which the authors were affiliated when the work was completed.
- For the corresponding author, please list: Full name, department, institution, city and state of location, and country and email address only; do not list the full mailing address, telephone, or fax numbers.

Authorship

The journal follows the ICMJE de nition of authorship, which indicates that authorship be based on the following 4 criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he or she has done, an author should be able to identify which co-authors are responsible for speci c other parts of the work. In addition, authors should have con dence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identi ed as authors. Those who do not meet all four criteria should be acknowledged. These authorship criteria are intended to reserve the status of authorship for those who deserve credit and can take responsibility for the work. The criteria are not intended for use as a means to disqualify colleagues from authorship who otherwise meet authorship criteria by denying them the opportunity to meet criterion #s 2 or 3. Therefore, all individuals who meet the rst criterion should have the opportunity to participate in the review, drafting, and nal approval of the manuscript.

Conflict of Interest Statement

Authors will be asked to provide a con ict of interest statement during the submission process. For details on what to include in this section, see the 'Con ict of Interest' section in the Editorial Policies and Ethical Considerations section below. Submitting authors should ensure they liaise with all co-authors to con rm agreement with the nal statement.

Abstract

1. Original submissions and brief reports, follow this structure.

    - Background: Brie y state the reason(s) or justi cation for undertaking the study. Objectives: Spell out the primary objective of the study. A hypothesis statement can also accompany an objective.
    - Methods: Begin by declaring the type of study design, time frame of study, population, and data source. Describe the primary exposure and outcome. Provide a brief description of analytic method, and how threats to study validity, including but not limited to, confounding, were addressed (if applicable). If space permits, declare alternate exposure de nitions and secondary outcome(s).
    - Results: Begin by providing the study size, exposure and outcome prevalence (or other appropriate descriptive measure). Statement of e ect measures (for the primary outcome) must be preceded by the outcome prevalence conditional on the exposure. Do not report Pvalues (see exceptions "P-value" section below); instead di erence and ratio measures must be accompanied by 95% con dence intervals.
    - Conclusion(s): Declare the primary nding of the study—if you have declared a hypothesis earlier, state if the study supports or does not support the

hypothesis. Conclusions should not be overstated, and do not present any new ndings here without declaring them in the “Results” section. Do not declare any policy-based implications or recommendations unless the study and/or the objective is policy-related. Causal language should be avoided unless fully supported by the design and statistical analysis.

2. Systematic reviews and meta-analysis, follow this structure.

- Background: Brie y state the reason(s) or justi cation for undertaking the study.
- Objectives: Spell out the primary and secondary objectives of the study.
- Data sources: List all data sources that were accessed to undertake the systematic review and/or meta-analysis.
- Study selection and data extraction: State explicitly the inclusion and exclusion criteria. How were data extracted from every study?
- Synthesis: Describe how the systematic review was performed and/or how the meta-analysis was accomplished. State how heterogeneity was assessed, and how data pooling was accomplished.
- Results: Begin by providing the number of eligible studies, total study size, as well as the prevalence of the exposure, and outcome. Statement of e ect measures (for the primary outcome) must be preceded by the outcome prevalence conditional on the exposure. Do not report P-values (see exceptions in the “P-value” section below); instead di erence and ratio measures must be accompanied by 95% con dence intervals. Where appropriate, provide an assessment of the inter- study heterogeneity (I2 statistic); and discuss the potential for associations to be a ected by publication bias.
- Conclusion(s): Declare the primary nding of the study; if you have declared a hypothesis earlier, state if the study supports or does not support the hypothesis. Conclusions should not be overstated, and do not present any new ndings here without declaring them in the “Results” section. Causal language should be avoided.

3. Study design papers, follow this structure.

- Background: Brie y state the reason(s) or justi cation for undertaking the study.
- Objectives: Spell out the primary and secondary objectives of the study.
- Population: State the population from which subjects were recruited (sampling base).
- Design: State the study design; be as explicit as possible.
- Methods: Describe the exposure(s) and primary and secondary outcome(s), and other relevant details.
- Preliminary results: Begin by stating the time frame of study, and provide a description of the cohort. Describe the primary exposure(s) and outcome(s). Provide details regarding recruitment and follow-up, and comment on loss to follow-up. If space permits, declare alternate exposure de nitions and secondary outcome(s).
- Conclusion(s): Declare the primary nding of the study. Conclusions should not be overstated, and do not present any new ndings here without declaring them in the "Results" section. Causal language should be avoided.

Synopsis

We require that you provide a brief synopsis of the paper of no more than 125 words, organised under the following headings.

- Study question.
- What's already known.
- What this study adds.

Keywords

Insert a set of 4-6 key words, separated by semicolons, on a new page after the abstract. Keywords should be taken from those recommended by the US National Library of Medicine's Medical Subject Headings (MeSH) browser list at www.nlm.nih.gov/mesh.

Word count

Provide a word count not including the abstract, tables, gures, or references after the keywords.

Main text

The required section headings (shown in bold) are as follows: **Background, Methods, Results, Comment, and Conclusions**.

The Methods section should include the following sub-sections:

- Cohort or case-control selection: Preferably with a ow chart describing all exclusions.
- Exposure (both primary and secondary).
- Outcomes (both primary and secondary).
- Statistical analysis: Clearly describe the general approach to statistical analyses and including the following to sub-sections.
    - Missing data (see below).
    - Sensitivity analyses (see below).
- Ethics approval: A sentence noting the institution(s) where ethics approval was obtained.

Manuscript Structure

The manuscript should contain the following sections, in the following order, with each section beginning on a new page: Title page, Synopsis, Abstract, Key words, Main text, References, Acknowledgements, Funding, Figure legends, Tables, Table legends, Figures, Supplemental tables, and Supplemental gures.

Acknowledgments

Contributions from anyone who does not meet the criteria for authorship should be listed, with permission from the contributor, in an Acknowledgments section. Any acknowledgements should be placed at the end of the text before the references. Authors should be sure that they have obtained permission to mention any individual acknowledged by name. Financial and material support should also be mentioned. Thanks to anonymous reviewers are not appropriate.

References

References in the text should be referred to by a superscript number after the punctuation. The list of references at the end of the manuscript should be listed in the order in which they appear in the text. Note that journal names should be spelt out in full, and both the beginning and the ending page numbers should be listed in full. References to personal communications, unpublished data or manuscripts “in preparation” should not be included. If essential, such material may be incorporated at the appropriate place in the text. The style should be as follows:

- For articles, give authors' names followed by initials, full title of the article, name of journal, year of publication, volume number, rst and last relevant page numbers. List all authors and if the number exceeds six give the rst six, followed by et al.

  Example: Sophist J, Paradigm K. The variation in infant sex ratio according to degree of maternal pedantry. International Journal of Perinatal Variation 1979; 7:143-152.

- For books, give authors' names followed by initials, title of chapter/article, title of book preceded by "In:," "Editor(s):" followed by name(s) and initial(s), place of publication, publisher's name, year of publication, rst and last relevant page numbers.

  Example: Cart A. Patterns of illness in children living in an area of heavy pollution. In: Horse Sense. Editors: Loh J, Mee K, Soh AH. Solihull: Khyber Press, 1984; pp. 14-83.

- We strongly recommend the use of a tool such as EndNote for reference management and formatting. EndNote reference styles can be found at: https://endnote.com/downloads/styles.

Tables

- Tables should only be prepared in Microsoft Word using the table function and created in a manner such that it is clear what is being shown.
- Tables should be clearly labelled and able to be understood apart from the text.
- Each table should begin on a separate sheet, numbered consecutively with Arabic numerals, containing only horizontal lines (one each at the top and bottom of the table and with additional lines to divide table sections only as needed), and with a concise legend. Table footnotes should be denoted with superscript lowercase letters.
- Aside from the column headings, none of the table entries should be in bold.
- Con dence intervals should be put in round brackets, separated by a comma not a dash.
- The reference category for relative measures of e ect should always be labelled as "1.00
- (Reference)" (not "ref"); for absolute measures, the reference category should be labelled as "0.00 (Reference)."

Figure Legends

Legends should be concise but comprehensive – the gure and its legend must be understandable without reference to the text. Include de nitions of any symbols used and de ne/explain all abbreviations and units of measurement.

Figures

- Authors' original artwork will be used; labelling should be in Calibri typeface, 12 points so that after reduction it is no smaller than eight points.
- All gures must be at least 300 × 300 DPI.
- Symbols and lines should be distinct after reduction; histograms should be black, white or hatched in distinctive ways; background lines should not be used. Legends for gures should be typed on a separate sheet.
- In the full-text online edition of the journal, gure legends may be truncated in abbreviated links to the full-screen version. Therefore, the rst 100 characters of any legend should inform the reader of key aspects of the gure.
- Complete guidance regarding the preparation and preferred le formats for gures and images are available at http://author services.wiley.com/bauthor/illustration.asp.

Supplemental Material

- We accept supplemental tables and gures that support the main analyses.
- All supplemental tables and gures must be referenced in the text as "eTable x" or "eFigure x."

Other Points to Consider

- Presenting a DAG to highlight the pathways amongst variables is highly recommended.
- Cohort, cross-sectional studies, or randomised controlled trials: always present relative risk/risk ratio orrate ratio (never odds ratios) or risk di erences, derived from log-linear regression models (see Spiegelman D, Hertzmark E. Easy SAS calculations for risk or prevalence ratios and di erences. American Journal of Epidemiology 2005 Aug 1;162 (3):199-200).
- Case-control studies: odds ratios are ne, but if sampling fractions of cases and controls are available,then present e ect measures from a weighted analysis, and so a relative risk/risk ratio or rate ratio is preferred.
- Standard deviations are preferred over standard errors for sample descriptions.
- Avoid statements such as "This was the rst study to…" or "We were the rst to…"

- When race, ethnicity, or nationality (de ned as place of birth) is identi ed as research variables, authorsshould make clear the purpose for using such variables. Authors should describe their methods of de nition and classi cation of racial, ethnic, or nationality groupings. Ethnocentricity should be avoided. For example, in choosing a reference group, it should not be assumed that the majority racial, or ethnic group is necessarily the best choice. Care should be taken to explain the choice of referent. Limitations of race, ethnicity, and nationality data and measurement should be clearly stated. Known or potential causes of the observed di erences between groups should be explored and discussed.
- Sex versus gender: We are cognisant of the fact that some people do not identify their gender as thebiological sex they were born with. We ask that authors be clear whether they are talking about biological sex or self-identi ed gender.

Data Citation

Please review Wiley's data citation policy here.

Additional Files

Appendices

Appendices will be published after the references. For submission they should be supplied as separate les but referred to in the text.

Supporting Information

Supporting information is information that is not essential to the article, but provides greater depth and background. It is hosted online and appears without editing or typesetting. It may include tables, gures, videos, datasets, etc.

Click here for Wiley's FAQs on supporting information.

Note: if data, scripts, or other artefacts used to generate the analyses presented in the paper are available via a publicly available data repository, authors should include a reference to the location of the material within their paper.

Wiley Author Resources

Manuscript Preparation Tips: Wiley has a range of resources for authors preparing manuscripts for submission available here. In particular, we encourage authors to consult Wiley's best practice tips on Writing for Search Engine Optimization.

Article Preparation Support

Wiley Editing Services o ers expert help with English Language Editing, as well as translation, manuscript formatting, gure illustration, gure formatting, and graphical abstract design – so you can submit your manuscript with con dence.

Also, check out our resources for Preparing Your Article for general guidance about writing and preparing your manuscript.

5. EDITORIAL POLICIES AND ETHICAL CONSIDERATIONS

Editorial Review and Acceptance

The acceptance criteria for all papers are the quality and originality of the research and its signi cance to our readership. Except where otherwise stated, manuscripts are single-blind peer reviewed. Papers will only be sent to review if the Editors-in-Chief determine that the paper meets the appropriate quality and relevance requirements.

Wiley's policy on con dentiality of the review process is available here.

Guidelines on Publishing and Research Ethics in Journal Articles Please review Wiley's policies surrounding human studies, animal studies, clinical trial registration, biosecurity, and research reporting guidelines here.

Con ict of Interest

The journal requires that all authors disclose any potential sources of con ict of interest. Any interest or relationship, nancial or otherwise that might be perceived as in uencing an author's objectivity is considered a potential source of con ict of interest. These must be disclosed when directly relevant or directly related to the work that the authors describe in their manuscript. Potential sources of con ict of interest include but are not limited to: patent or stock ownership, membership of a company board of directors, membership of an advisory board or committee for a company, and consultancy for or receipt of speaker's fees from a company. The existence of a con ict of interest does not preclude publication. If the authors have no con ict of interest to declare, they must also state this at submission. It is the responsibility of the corresponding author to review this policy with all authors and collectively to disclose with the submission ALL pertinent commercial and other relationships.

Funding

Authors should list all funding sources in the Acknowledgments section. Authors are responsible for the accuracy of their funder designation. If in doubt, please check the Open Funder Registry for the correct nomenclature: https://www.crossref.org/services/funder-

registry/. Please list all funding sources, including the grant or contract number and the funding agency

Missing data

- Multiple imputation methods are required so long as the pattern of missing data satis es the assumptions required for imputations, with a minimum of 50 imputations.
- Please describe exactly the proportion of missing data for individual variables, how multiple imputation was performed and all other relevant details. Providing citations will be preferred.
- Multiple imputation is generally not necessary when missing data are <5%.

Sensitivity analysis

Most observational studies su er from two common biases: selection bias and unmeasured confounding. We ask that authors undertake and report additional sensitivity analysis that addresses the following biases.

- Selection bias: Authors should provide a ow diagram to describe the exclusion categories and loss to follow-up. Authors must explicitly address selection bias by describing the characteristics of included versus excluded groups and the potential impact on results, including using statistical techniques, such as inverse probability weighting, when appropriate.
- Unmeasured confounding: An additional requirement for the estimation of causal e ects requires that the associations remain una ected by unmeasured confounding. We ask authors to undertake a sensitivity analysis to address unmeasured confounding through the "E-value" method, described in VanderWeele TJ, Ding P. Sensitivity analysis in observational research: Introducing the "E-Value." Annals of Internal Medicine 2017;167(4):268-274.

Material and Methods

If a method or tool is introduced in the study, including software, questionnaires, and scales, the author should state the license this is available under and any requirement for permission for use. If an existing method or tool is used in the research, the authors are responsible for checking the license and obtaining the permission. If permission was required, a statement con rming permission should be included in the Material and Methods section.

The Comment section should include the following sub-headings:

- Principal ndings
- Strengths of the study

- Limitations of the data
- Interpretation
- Conclusions

Data Sharing and Data Accessibility

Please review Wiley's policy here.This journal encourages data sharing.

The journal encourages authors to share the data and other artefacts supporting the results in the paper by archiving it in an appropriate public repository. Authors should include a data accessibility statement, including a link to the repository they have used, in order that this statement can be published alongside their paper.

Human subject information in databases

The journal refers to the World Health Medical Association Declaration of Taipei on Ethical Considerations Regarding Health Databases and Biobanks.

Publication Ethics

This journal is a member of the ,a href="https://publicationethics.org/">Committee on Publication Ethics (COPE). Note this journal uses iThenticate's CrossCheck software to detect instances of overlapping and similar text in submitted manuscripts. Read Wiley's Top 10 Publishing Ethics Tips for Authors here. Wiley's Publication Ethics Guidelines can be found here.

ORCID

Please see Wiley's resources on ORCID here.

As part of our commitment to supporting authors at every step of the publishing process, Paediatric and Perinatal Epidemiology requires the submitting author (only) to provide an ORCID iD when submitting a manuscript. This takes around 2 minutes to complete. Find more information.

6. AUTHOR LICENSING

If your paper is accepted, the author identi ed as the formal corresponding author will receive an email prompting them to log in to Author Services, where via the Wiley Author Licensing Service (WALS) they will be required to complete a copyright license agreement on behalf of all authors of the paper.

Authors may choose to publish under the terms of the journal's standard copyright agreement, or Open Access under the terms of a Creative Commons License.

General information regarding licensing and copyright is available here. To review the Creative Commons License options o ered under Open Access, please click here. (Note that

certain funders mandate that a particular type of CC license has to be used; to check this please click here.)

Self-Archiving de nitions and policies. Note that the journal's standard copyright agreement allows for self-archiving of di erent versions of the article under speci c conditions. Please click here for more detailed information about self-archiving de nitions and policies.

Open Access fees: If you choose to publish using Open Access you will be charged a fee. A list of Article Publication Charges for Wiley journals is available here.

Funder Open Access: Please click here for more information on Wiley's compliance with speci c Funder Open Access Policies.

7. PUBLICATION PROCESS AFTER ACCEPTANCE

Accepted article received in production

When your accepted article is received by Wiley's production team, you (corresponding author) will receive an email asking you to login or register with Author Services. You will be asked to sign a publication license at this point.

Accepted Articles

The journal o ers Wiley's Accepted Articles service for all manuscripts. This service ensures that accepted

'in press' manuscripts are published online very soon after acceptance, prior to copy-editing or typesetting. Accepted Articles are published online a few days after nal acceptance, appear in PDF format only, are given a Digital Object Identi er (DOI), which allows them to be cited and tracked, and are indexed by PubMed. After publication of the nal version article (the article of record), the DOI remains valid and can continue to be used to cite and access the article.

Accepted Articles will be indexed by PubMed; submitting authors should therefore carefully check the names and a liations of all authors provided in the cover page of the manuscript so it is correct for indexing. Subsequently the nal copyedited and proofed articles will appear in an issue on Wiley Online Library; the link to the article in PubMed will automatically be updated.

Proofs

Authors will receive an e-mail noti cation with a link and instructions for accessing HTML page proofs online. Page proofs should be carefully proofread for any copyediting or typesetting errors. Online guidelines are provided within the system. No special software is

required, all common browsers are supported. Authors should also make sure that any renumbered tables, gures, or references match text citations and that gure legends correspond with text citations and actual gures. Proofs must be returned within 48 hours of receipt of the email. Return of proof via e-mail is possible in the event that the online system cannot be used or accessed.

Major alterations to the text, tables, and gures are only allowed in exceptional circumstances, and the additional cost may be charged to the author. Such changes must be approved by the Editor-in- Chief.

Early View

The journal o ers rapid publication via Wiley's Early View service. Early View (Online Version of Record) articles are published on Wiley Online Library before inclusion in an issue. Note there may be a delay after corrections are received before your article appears online, as Editors also need to review proofs. Once your article is published on Early View no further changes to your article are possible. Your Early View article is fully citable and carries an online publication date and DOI for citations.

8. POST PUBLICATION

Access and sharing

When your article is published online:

- You receive an email alert (if requested).
- You can share a link to your published article through social media.
- As the author, you will have free access to your paper (after accepting the Terms & Conditions of use,you can view your article).
- The corresponding author and co-authors can nominate up to ten colleagues to receive a publicationalert and free online access to your article. You can now order print copies of your article (instructions are sent at proo ng stage or use the website indicated below). www.sheridan.com/wiley/eoc

Wiley's Author Name Change Policy

In cases where authors wish to change their name following publication, Wiley will update and republish the paper and redeliver the updated metadata to indexing services. Our editorial and production teams will use discretion in recognizing that name changes may be of a sensitive and private nature for various reasons including (but not limited to) alignment with gender identity, or as a result of marriage, divorce, or religious conversion. Accordingly, to protect the author's privacy, we will not publish a correction notice to the

paper, and we will not notify co-authors of the change. Authors should contact the journal's Editorial O ce with their name change request.

Article Promotion Support

Wiley Editing Services o ers professional video, design, and writing services to create shareable video abstracts, infographics, conference posters, lay summaries, and research news stories for your research – so you can help your research get the attention it deserves.

Cover Image Submissions

This journal accepts artwork submissions for Cover Images. This is an optional service you can use to help increase article exposure and showcase your research. For more information, including artwork guidelines, pricing, and submission details, please visit the Journal Cover Image page.

Measuring the Impact of your Work

Wiley also helps you measure the impact of your research through our specialist partnerships with Kudos and Altmetric.

Archiving Services

Portico and CLOCKSS are digital archiving/preservation services we use to ensure that Wiley content will be accessible to customers in the event of a catastrophic event such as Wiley going out of business or the platform not being accessible for a signi cant period of time. Member libraries participating in these services will be able to access content after such an event. Wiley has licenses with both Portico and CLOCKSS, and all journal content gets delivered to both services as it is published on Wiley Online Library. Depending on their integration mechanisms, and volume loads, there is always a delay between content being delivered and showing as "preserved" in these products.

9. EDITORIAL OFFICE CONTACT DETAILS

For queries about submissions, please contact PPEo ce@wiley.com

Transferable Review: Health Science Reports

This journal works together with Wiley's Open Access Journal, Health Science Reports to enable rapid publication of good quality research that is unable to be accepted for publication by our journal. Authors may be o ered the option of having the paper, along with any related peer reviews, automatically transferred for consideration by the Editor of Health Science Reports. Authors will not need to reformat or rewrite their manuscript at this stage, and publication decisions will be made a short time after the transfer takes place. The Editor of Health Science Reports will accept submissions that report wellconducted research that

reaches the standard acceptable for publication. Health Science Reports is a Wiley Open Access journal which is indexed on PubMed/MEDLINE and Scopus. For more information please go to www.healthsciencereports.org.