Machine Learning Models for Predicting Neonatal Mortality: A Systematic Review

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Keywords

Artificial intelligence · Neonate · Mortality · Systematic review

Abstract

Introduction: Approximately 7,000 newborns die every day, accounting for almost half of child deaths under 5 years of age. Deciphering which neonates are at increased risk for mortality can have an important global impact. As such, integrating high computational technology (e.g., artificial intelligence [AI]) may help identify the early and potentially modifiable predictors of neonatal mortality. Therefore, the objective of this study was to collate, critically appraise, and analyze neonatal prediction studies that included AI. **Methods:** A literature search was performed in PubMed, Cochrane, OVID, and Google Scholar. We included studies that used AI (e.g., machine learning (ML) and deep learning) to formulate prediction models for neonatal death. We excluded small studies ($n < 500$ individuals) and studies using only antenatal factors to predict mortality. Two independent investigators screened all articles for inclusion. The data collection consisted of study design, number of models, features used per model, feature importance, internal and/or external validation, and calibration analysis. Our primary outcome was the average area under the receiving characteristic

curve (AUC) or sensitivity and specificity for all models included in each study. **Results:** Of 434 articles, 11 studies were included. The total number of participants was 1.26 M with gestational ages ranging from 22 weeks to term. Number of features ranged from 3 to 66 with timing of prediction as early as 5 min of life to a maximum of 7 days of age. The average number of models per study was 4, with neural network, random forest, and logistic regression comprising the most used models (58.3%). Five studies (45.5%) reported calibration plots and 2 (18.2%) conducted external validation. Eight studies reported results by AUC and 5 studies reported the sensitivity and specificity. The AUC varied from 58.3% to 97.0%. The mean sensitivities ranged from 63% to 80% and specificities from 78% to 99%. The best overall model was linear discriminant analysis, but it also had a high number of features ($n = 17$). **Discussion/Conclusion:** ML models can accurately predict death in neonates. This analysis demonstrates the most commonly used predictors and metrics for AI prediction models for neonatal mortality. Future studies should focus on external validation, calibration, as well as deployment of applications that can be readily accessible to health-care providers.

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Introduction

Neonatal mortality contributes significantly to childhood death rates. According to the World Health Organization, neonates comprise 47% of deaths among children <5 years of age [1]. Therefore, one of the goals of the USA is to reduce worldwide neonatal death by the year 2030 [2]. Identifying factors leading to neonatal deaths may guide future areas for intervention and could assist clinicians when discussing potential outcomes with families.

Artificial intelligence (AI) is an expanding area of research in the medical field. Specifically, machine learning (ML) is a branch of AI that is capable of performing complex tasks that typically require human intelligence. ML approaches recognize patterns, create algorithms, and adapt according to the new data [3]. Compared to traditional logistic/linear regression techniques, ML methods can unravel interactions that are nonlinear or binary and can yield highly stable predictions in large datasets that are oftentimes challenging to find correlations [4]. Furthermore, there are voluminous number of models from which to choose in ML that allows for an optimal algorithm within the same data (e.g., artificial neural networks, random forest, least discriminant analysis, k-nearest neighbor, and even logistic regression [LR] [3, 5, 6], refer to Figure 1 for a summary comparing traditional statistical methods compared to ML).

Integration of high computational algorithms into the health-care system has improved patient care, safety, and hospital efficiency. For instance, a recent article used computer modeling to inform which in-patient surgical patients were more likely to be discharged within 24 h [7]. Another example is the use of AI in intensive care units (ICUs), to alarm providers which patients are at increased risk for sepsis. Notably, similar algorithms have been used to investigate risk factors for death in neonates.

Our interest was to review neonatal studies that used AI models to identify risk factors for deaths. We chose to study AI as this emerging field can analyze complex relationships and recognize patterns to optimize predictive abilities. Thus, we conducted a systematic review to synthesize and examine the predictive ability of AI-based algorithms for neonatal mortality.

Methods

This review adhered to the guidelines set by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement, refer to online suppl. File 1; for all online suppl. material, see www.karger.com/doi/10.1159/000516891 [8]. Our protocol was

registered to PROSPERO, the international prospective register of systematic reviews on February 17, 2021; refer to online suppl. File 2.

Literature Search

A literature search was performed using MEDLINE's database PubMed, OVID, and Cochrane through December 16, 2020. Search terms included "neonate," "newborn," "infant," "mortality," "death," "artificial intelligence," "machine learning," and "deep learning." Peer-reviewed articles were included. A filter was placed to limit the studies to humans and children. More details can be viewed in online suppl. File 3. Two investigators (S.Z. and C.M.) screened titles and abstracts from the search results and then independently reviewed full-text articles that met inclusion criteria. A third investigator (A.M.) was utilized to resolve any differences in the article selection (see online suppl. File 4 for more details).

Inclusion and Exclusion Criteria

In this study, neonatal death was described as death within the first 28 days of life per the definition by the World Health Organization [9]. We included all live-born infants, irrespective of pre-term or term gestation. For studies including premature newborns, the outcome of mortality was assessed until they were discharged from the hospital. Studies were eligible if they included AI-based algorithms (e.g., ML, deep learning, neural network, etc.) to predict neonatal death. Prospective and retrospective studies that examined both perinatal factors and neonatal factors were included. Studies were excluded if they used only antenatal factors to predict perinatal death or stillborn. Also, studies were not included if neonatal mortality was not the primary outcome of the study or if the term newborns died outside the neonatal period. The studies were excluded that had <500 patients due to ML models having less accuracy in smaller datasets [10, 11].

Primary End Point and Data Extraction

The primary end point for this study was mortality during the neonatal period. The data were collected by all investigators and compared for accuracy, with an additional investigator who resolved any differences. The additional investigator was utilized on 3 occasions to help resolve the differences during the extraction of data due to ambiguous reporting in study methodologies. The extracted data included the study design (sample size, type of ML model, exclusion criteria, timing of the data, and handling of missing data), ML data (number of variables examined, number of variables in the final models, the variables used in the models, performance metrics, percent of data used to test, train, or internally validate the model, cross-validation, calibration, hyperparameter tuning, and external validation), and if studies compared models to LR. All models used to predict were included (e.g., studies reporting multiple ML models with different combinations of predictors).

Performance Metrics and Data Analysis

Numerous metrics are typically used in prediction models formulated via AI. The area under the receiver operating characteristic curve (AUC) is the most widely used test to assess the predictive ability of a model. The AUC is a graphic interpretation that incorporates sensitivity (true positive/true positive + false negative) and specificity (true negative/true negative + false positive). We chose

Fig. 1. Flow diagram of model development. Side by side comparison of ML and LR. ML, machine learning; LR, logistic regression; PPV, positive predictive value.

AUC, a priori, as the performance metric. If the study did not report the AUC, we collected the sensitivity and specificity as they are surrogates for the AUC. Since the confidence interval of the AUC was not uniformly reported, we computed the mean with standard deviation (SD) of the AUC for all the prediction models included in each study. This technique has been used in similar systematic reviews [12, 13]. All analyses and graphics were conducted in R version 4.0.4.

Risk of Bias

Risk of bias for each study was evaluated independently by 2 investigators, with a third investigator who acted as a tiebreaker if there were any differences. Risk of bias was assessed with the Checklist for Critical Appraisal and Data Extraction for System-

atic Reviews of Prediction Modeling Studies checklist [14]. Level of evidence for the 9 domains was expressed as high, low, or unclear. Reviews of ML studies have identified the underreporting of experimental methods as a source of potential bias as variables can be weighed to heavily or models can be overfitting the data [15, 16].

Results

Study Selection

After identifying articles through the various databases and checking articles' references for additional studies,

Fig. 2. Flow diagram for study selection.

a total of 484 articles were screened. After screening and removal of duplicates, a total of 29 full-text articles were read and 11 articles met inclusion criteria [17–27]. Reasons for exclusion are described in the flow diagram in Figure 2.

Study Characteristics

All study populations were taken from various countries, all of which were from North America and Europe. The number of patients in each dataset ranged widely, with a median sample of 850. The complete study characteristics can be seen in Table 1.

The studies reported a total of 129 different models, ranging from 1 to 52 models per article. Gilchrist et al. used 2 datasets for their study, one of the sets had <500 patients, so the 7 models derived from the small dataset were excluded. The number of features per model ranged

from 2 to 66. Of the 11 studies, 9 (82%) created >1 model. All studies reported the time period over which the data were collected which ranged from collection at delivery through entire hospital stay. A majority of the studies (73%) reported exclusion criteria for the study.

Handling of missing values was reported in 81.8% of the articles; the handling of missing data was done by removal of incomplete cases or simple imputation of missing values. Model calibration, hyperparameter tuning, and external validation were done in <50% of the articles. Cross-validation was utilized in 73% of the studies.

Model Design

The most common ML algorithms were artificial neural networks, LR, and random forest. Traditionally, LR is the most common algorithm for prognostic modeling and therefore often compared to AI-based models [28].

Table 1. Summary of study characteristics

Reference	Geographic area	Sample size	Final number or range of included features	Time of data collection	Exclusion criteria	Handling of missing values	Hyperparameter tuning	Validation	Calibration	Types of prediction models	Prediction models, <i>n</i>	Log regression comparison (ML vs. Trad)
Ambalavanan et al. [17]	USA	810	7–23	6 HOL	Infants who died in the delivery room	Not reported	No	Training, test, validation split	Yes	ANN, LR	4	Yes (Trad)
Ambalavanan et al. [18]	USA	8,608	3–28	Delivery through 7 DOL	Infants ≤ 400 or $> 1,000$ g	Removal of incomplete cases	No	10-fold CV	Yes	ANN, LR	10	Yes (ML)
Frize et al. [19]	Canada	634	13	Admission to 48 h	Not reported	Imputed missing values by hybrid ANN-CBR approach	No	5 $\times$ 2-CV and external	Not reported	ANN	1	No
Frize et al. [20]	Canada	2 datasets: (a) 506 (b) 630	3–18	48 h after admission	Not reported	Imputed missing values by hybrid ANN-CBR approach	No	5 $\times$ 2-CV	Not reported	ANN RFW, ANN 4 builder	4	No
Gilchrist et al. [21]	Canada	2 datasets: (a) 17,364 (b) Excluded since < 500	18	12 HOL	Excluded patient records missing $> 50\%$ of the attributes	Removed patients missing $> 50\%$ of the attributes, model uses a probabilistic algorithm to handle missing data	No	5 $\times$ 2-CV	Not reported	C5 decision tree	8 (7 models excluded due to < 500 patients in dataset)	No
Kefi et al. [27]	USA	800	17–31	Admission to 2 h	Any readmissions to NICU	Removed variables with $> 50\%$ of missing data, replaced missing data with mean value	No	10-fold CV	Not reported	LR, LDA, KNN, CART, NB, SVM, RF	14	Yes (ML)
Liu et al. [22]	USA	710,471	66	Delivery record	Infants with GA < 23 and > 37 wk	Simple imputation of missing data	Yes	10-fold CV	Yes (brier test)	LR, cRF, rRF, BART	52	Yes (Trad)
Podda et al. [23]	Italy	23,747	12	5 MOL	Infants < 22 wk or with congenital anomalies, or missing values for any predictors	Excluded infants with missing data	Yes	5-fold CV and external	Yes (brier test)	LR, KNN, GBM, RF, SVM, ANN	6	Yes (ML)
Shukla et al. [24]	South Asia, Africa, Latin America	481,058	15	Delivery/Day 1 and postdelivery/Day 2	Stillbirths, deaths on DOL 0, miscarriages, participants enrolled after delivery	Excluded cases with missing data	Yes	10-fold CV	Not reported	SVM, EN, LR, RF, GBE, ANN	12	Yes (Trad)
Townsend and FrizeCanada [25]	Canada	15,384	18	12 h after admission	Not reported	Missing values imputation by KNN	No	Training, test, validation split	Yes	ANN	1	No
Zernikow et al. [26]	Germany	890	2–13	At admission	Infants with GA > 32 and/or BW $< 1,500$ g	Not reported	No	External validation	Not reported	ANN, LR	17	Yes (ML)

ML, machine learning; Trad, traditional; MOL, minutes of life; HOL, hours of life; DOL, days of life; GA, gestational age; BW, birthweight; CV, cross-validation; ANN, artificial neural network; LR, logistic regression; ANN-CBR, artificial neural network-case based reasoning; ANN RFW, artificial neural network research framework; LDA, linear discriminant analysis; KNN, K-nearest neighbors; CART, classification and regression trees; NB, naive Bayes; SVM, support vector machine; RF, random forest; BART, Bayesian additive regression trees; cRF, classification random forest; rRF, regression random forest; GBM, gradient boosting machine; EN, logistic elastic net; GBE, gradient boosting ensemble.

Table 2. Summary of model performance

Reference	Model type	Features, <i>n</i>	Timing of data collection	AUC	Sensitivity, %	Specificity, %
Podda et al. [23]	LR	12	5 MOL	0.9098	NR	NR
	KNN	12	5 MOL	0.9108	NR	NR
	RF	12	5 MOL	0.9138	NR	NR
	GDM	12	5 MOL	0.9147	NR	NR
	SVM	12	5 MOL	0.9147	NR	NR
	ANN	12	5 MOL	0.9149	NR	NR
Shukla et al. [24]	SVM	15	Delivery/Day 1	0.583	NR	NR
	EN	15	Delivery/Day 1	0.81	NR	NR
	LR	15	Delivery/Day 1	0.81	NR	NR
	RF	15	Delivery/Day 1	0.82	NR	NR
	GBE	15	Delivery/Day 1	0.825	NR	NR
	ANN	15	Delivery/Day 1	0.83	NR	NR
	SVM	15	Postdelivery/Day 2	0.61	NR	NR
	EN	15	Postdelivery/Day 2	0.85	NR	NR
	LR	15	Postdelivery/Day 2	0.85	NR	NR
	RF	15	Postdelivery/Day 2	0.87	NR	NR
	GBE	15	Postdelivery/Day 2	0.87	NR	NR
	ANN	15	Postdelivery/Day 2	0.86	NR	NR
Townsend and Frize [25]	ANN	18	12 HOL	0.907	70.5	92.6
Zernikow et al. [26]	ANN	13	At admission	0.954	NR	NR
	ANN	12	At admission	0.924	NR	NR
	ANN	12	At admission	0.928	NR	NR
	ANN	12	At admission	0.929	NR	NR
	ANN	12	At admission	0.930	NR	NR
	ANN	12	At admission	0.936	NR	NR
	ANN	12	At admission	0.943	NR	NR
	ANN	12	At admission	0.945	NR	NR
	ANN	12	At admission	0.945	NR	NR
	ANN	12	At admission	0.946	NR	NR
	ANN	12	At admission	0.947	NR	NR
	ANN	12	At admission	0.947	NR	NR
	ANN	12	At admission	0.949	NR	NR
	ANN	12	At admission	0.950	NR	NR
	ANN	11	At admission	0.881	NR	NR
	ANN	2	At admission	0.890	NR	NR
	LR	6	At admission	0.917	NR	NR
Ambalavanan et al. [17]	ANN	7	6 HOL	0.87	80	85
	ANN	23	6 HOL	0.83	80	69
	LR	7	6 HOL	0.87	80	85
	LR	23	6 HOL	0.82	80	72
Frize et al. [19]	ANN	13	Adm to 48 h	NR	63	99
Frize et al. [20]	ANN RFW	3	48 h after adm	NR	62	99
	ANN RFW	18	48 h after adm	NR	68	97
	ANN builder	3	48 h after adm	NR	72	96
	ANN builder	18	48 h after adm	NR	81	98
Gilchrist et al. [21]	C5 decision tree	18	12 HOL	NR	56	97

Table 2 (continued)

Reference	Model type	Features, <i>n</i>	Timing of data collection	AUC	Sensitivity, %	Specificity, %
Kefi et al. [27]	LR	17	Adm to 2 h	0.86	NR	NR
	LDA	17	Adm to 2 h	0.96	NR	NR
	KNN	17	Adm to 2 h	0.97	NR	NR
	CART	17	Adm to 2 h	0.71	NR	NR
	NB	17	Adm to 2 h	NR	NR	NR
	SVM	17	Adm to 2 h	0.74 (L)/0.89 (P)	NR	NR
	RF	17	Adm to 2 h	0.80	NR	NR
	LR	31	Adm to 2 h	0.91	NR	NR
	LDA	31	Adm to 2 h	0.97	NR	NR
	KNN	31	Adm to 2 h	0.57	NR	NR
	CART	31	Adm to 2 h	0.64	NR	NR
	NB	31	Adm to 2 h	NR	NR	NR
	SVM	31	Adm to 2 h	0.84 (L)/0.83 (P)	NR	NR
	RF	31	Adm to 2 h	0.86	NR	NR
Liu et al. [22]	LR cRF	66	Delivery record	0.924*	NR	NR
	rRF	66	Delivery record	0.939*	NR	NR
	BART	66	Delivery record	0.940*	NR	NR
		66	Delivery record	0.947*	NR	NR

MOL, minutes of life; HOL, hours of life; DOL, days of life; ANN, artificial neural network; LR, logistic regression; ANN-CBR, artificial neural network-case based reasoning; ANN RFW, artificial neural network research framework; LDA, linear discriminant analysis; KNN, K-nearest neighbors; CART, classification and regression trees; NB, naive Bayes; SVM, support vector machine; RF, random forest; BART, Bayesian additive regression trees; cRF, classification random forest; rRF, regression random forest; GBM, gradient boosting machine; EN, logistic elastic net; GBE, gradient boosting ensemble; NR, not reported; AUC, area under the receiving characteristic curve.

*Average c-statistic of all 13 years.

However, this should not be confused with a LR ML approach. Of the studies examined, 4 studies (36%) compared AI-based models to machine learning LR models [18, 23, 26, 27]. Three studies (27%) compared ML to the traditional LR approach [17, 22, 23].

Model Performance

Table 2 shows a summary of model performance. Of the 11 studies, 8 (73%) reported the AUC. Two articles presented the data with sensitivity, specificity, positive predictive value, and negative predictive value. One article presented the data with only sensitivity and specificity [20]. Most of the prediction models were calculated in the first 48 h after the neonate was born.

Figure 3 graphically shows the average AUC with SD by study where the boxes show the calculated average AUC, with lines to identify SD and dots to represent AUC outliers. As seen, the mean AUC for the models in the 8 studies that reported AUC were above 70%. Two models had an average AUC >90% [22, 26]. Table 2 reports the sensitivity and specificity for 5 studies. The sensitivity was lower in 9 of the 11 models that included sensitivity and specificity. The model with highest sensitivity and speci-

ficity was by Frize et al. [20] which was an artificial neural network with 18 features and a sensitivity and specificity of 81 and 98%, respectively.

In Figure 4, we show the most common predictors accounted for in the studies. The top 4 predictors, also referred to as features, were birthweight, gestational age, Apgar score(s), and multiple births. These predictors were incorporated in at least 7 studies (64%). The K-nearest neighbor and least discriminant models by Kefi et al. [27], with 17 and 31, respective features, had the highest AUC at 97.0%. The model with the least number of features and highest AUC was a neural network model built by Ambalavanan et al. [18], which had an AUC of 81.6% and used only 3 variables (prenatal steroids, non-Hispanic blacks, and gestational age).

Risk of Bias

Currently, there is no widely used tool to assess risk of bias in ML models. For this review, the Checklist for critical Appraisal and data extraction for systematic Reviews of prediction Modeling Studies were used to assess for the risk of bias [14]. Online suppl. File 5 shows the areas where bias was assessed and whether there was high risk,

Fig. 3. Average AUC with SD by study. Box and whisker plot displaying average AUC and calculated SD for the 8 studies that reported the AUC. Dots represent outliers. AUC, area under the receiving characteristic curve; SD, standard deviation.

low risk, or unknown risk of bias. All articles had low risk of bias in the areas of data source, outcomes, model performance, and model evaluation. The areas with the most concern for high risk of bias included the handling of missing data and result presentations. The studies where high risk due to limited reporting sample size data, the handling of missing data in the model, and the reporting of the results of the model, and how the results accounted for or adjusted for any missing data.

Discussion/Conclusion

AI or ML models have paved their way into research because of their ability to recognize complex, nonlinear patterns not otherwise identified by standard methods. There have been many ML models published in adult

studies, including those predicting death in a multitude of disease processes [29–33]. To date, there are far fewer AI models published in pediatrics and neonatology. To our knowledge, this is the first study to systematically review and analyze the published ML models predicting death in neonates.

Herein, we conducted a systematic review of 11 studies evaluating the predictive ability of AI models for neonatal mortality. This report included a total of 1.26 million infants with gestational ages ranging from 22 weeks to term. The mean AUC in this review varied from 58.3 to 97.0% demonstrating their ability to predict mortality in neonates. Despite several advantages of AI for medical prognostication, it is important to recognize the limitations of these techniques. Notwithstanding novel AI models, LR is, in itself, a very powerful tool, even for complex problems, and has been shown to yield comparable predictive performances when used in large population datasets [34]. In this report, the few AI-based algorithms comparing to non-AI-based (e.g., LR) models yielded similar AUC performance.

This review analyzed neonatal prediction models according to the AUC. The AUC, also referred to as C-statistic, is the most common performance measure in describing the discriminative performance of generalized LR/ LR models [35, 36]. While there is limited research on what specifically defines low versus high discriminative power, Steyerberg et al. [37] claim that models with an AUC around 60% as having low discriminative power versus high discriminative models having an AUC closer to 95%. Based on these criteria, only 5 of the models in the review had AUCs of 95% or higher, these were from Kefi et al. [27] and Zernikow et al. [26] with a range of 12–31 features and were models derived from linear discriminant analysis, K-nearest neighbor, and artificial neural network.

Five articles presented the sensitivities and specificities. The mean sensitivities ranged from 63 to 80% and specificities from 78 to 99%. Tests that are both highly sensitive and specific, generally those >70%, can indicate clinical utility for the accurate detection of positive and negative results [38]. Of the 11 models that included sensitivity and specificity, only 6 of said models had both sensitivity and specificity above 70%. Those models came from Ambalavanan et al. [17], Frize et al. [20], and Townsend and Frize [25] with a range of 3–18 features, and most were derived from artificial neural networks.

A fair amount of heterogeneity existed among the articles with regard to their validation tools. Only 48% of studies calibrated their models and an even smaller per-

Fig. 4. Frequency of features used by studies. Bar plot displaying features used in included articles according to number of occurrences.

centage (27%) performed external validation. An article by Liu et al. [3] stresses the importance of model validation and reproducibility. In order for a model to achieve universal applicability, it needs to be tested on a dataset outside of its own. Although a model might perform well on its own test data, the true performance of such a model is only known after it is applied to multiple new and unique datasets.

Although this review focused on AI models for mortality, multiple opportunities exist wherein AI can be integrated into the neonatal ICU. In the adult ICU, Awad and colleagues developed a ML model that outperformed highly validated clinical scoring systems [39]. In adult medicine, ML prediction models are now integrated into several electronic medical records that flag providers and/or deliver a quantitative risk for developing a future morbidity [40–43]. In a study of 31,000 ICU admissions, Nemati et al. [44] derived an AI prediction model that accurately predicted onset of sepsis up to 12 h prior to clinical recognition. Another potential area wherein AI can be incorporated in the NICU includes radiograph interpretation. After training an AI algorithm with >300,000 chest radiographs, the ability to interpret 72 different findings was comparable to upper level radiology residents [45]. Given that these conditions develop over time, predictive models will improve as more datapoints are fed into the algorithm.

Limitations

While this study was one of the first of its kind in examining ML and neonatal mortality, it does have some limitations. The first limitation was due to the limited number of articles available on this subject matter and the low quality of methodology reporting in many, this limits the amount of evidence that can be derived. Another issue throughout the articles was the reporting of the details of the dataset used and the ML model development not being consistent throughout the article. The variable nature and inconsistency of reporting in ML studies have been noted to be a problem in previous systematic reviews that examined ML [12, 46]. Other limitations regard the reporting of the summary measure from the articles, some presented the AUC while others presented the sensitivity and specificity. Without consistent metrics, it limits the ability to compare the studies and models to one another. The authors of this study did not reach out to the authors of the articles included in this study to try and obtain consistent metrics for all the included studies. The last limitation of the

study was the inconsistencies with which the included studies reported either a SD or confidence interval for their metrics, with multiple articles not reporting either.

Conclusion

In conclusion, machine learning models are capable of predicting neonatal deaths. Variability exists with regard to measurement of the model performance, handling of missing data, and validating tools. Less than half of the studies calibrated their models and less than one-third performed external validation. Future studies should focus on external validation, calibration, and deployment of applications that can be readily accessible to health-care providers.

Statement of Ethics

This study is exempt from Ethics Committee approval since it is a systematic review and only uses previously published literature and does not have any collected patient data.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

C.M. and S.Z. participated in the study design and carried out the data collection, assembled tables, risk of bias, and manuscript writing. K.T. performed the risk of bias. K.C. carried out the data collection and manuscript writing. Ax.M. carried out the data collection. A.M. participated in the study design, advised and carried out data to be collected, supervised all activities, all statistical computations, and the final manuscript drafting. All the authors provided feedback and approved the final manuscript.

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