




Review Article

Reducing False Alarms in Intensive Care Units: A Scoping Review



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Abstract

Background and objectives: Excessive false alarms in intensive care units (ICU) cause noise disturbance to patients and develop alarm fatigue among nurses, leading to safety concerns and decreased patient care quality. Evidence-based false alarm reduction strategies are urgently needed in the day-to-day clinical practice. This review aims to synthesize two main human-technology approaches to reduce false alarms generated by the physiologic monitor: customization of alarm settings by nurses and alarm algorithms.

Methods: A broad search was performed using four electronic databases, PubMed, Scopus, EMBASE, and Cumulative Index to Nursing and Allied Health Literature. This review included twenty-eight full-text journal articles focused on both customizations of alarm settings and alarm algorithm improvement for false alarm reduction in the ICU.

Results: Clinical customizations of alarm settings on bedside physiological monitors helps to reduce excessive false alarms. Colleagues also developed alarm algorithms to reduce false alarms in the ICU and achieved excellent performance.

Conclusions: This review suggests collaboration between nurses and engineers to optimize personalized machine learning algorithms has the great potential for false alarm reduction in the ICU.

Introduction

Excessive false clinical alarms compromise patient care and safety in intensive care units (ICU). Critical care nurses identified alarms

from cardiopulmonary physiologic monitors are one of the most helpful in the ICU, and yet the monitors also contribute to the highest numbers of false alarms,^{1,2} leading to the sensory overload at work. The bedside physiologic monitors have embedded alarm systems to alert clinicians to life-threatening and imminent changes in a patient's condition or device malfunction.³ However, it is well known that up to 94% of alarms were false positives or clinically irrelevant.⁴⁻⁷ These unnecessary false or irrelevant alarms have reached a noise peak of over 80 dB creating a noisy and annoying environment for both nurses and patients.^{8,9} Noise pollution from false alarms is viewed to be the most stressful noise in the ICU.¹⁰ It hinders patient recovery and quality of care. Moreover, constant demand and mistrust of the alarm system reduce the alertness of the clinicians leading to alarm fatigue. Alarm fatigue has resulted in desensitization to alarms which compromise patient safety,¹¹ including deaths, permanent loss of function, and unexpected additional care or extended stay. A high number of false alarms remained an unresolved issue in clinical practice.¹²

There are three categories of false alarms – clinical false alarms,

Keywords: Intensive care units; Clinical alarm; Artificial intelligence; Machine learning; Deep learning.

Abbreviations: BP, backpropagation; CEASE, Communication, Electrodes, Appropriateness, and Setup alarm parameters, and Education; CINAHL, Cumulative Index to Nursing and Allied Health Literature; CNN, convolutional neural networks; DFO, dispersive files optimization; ECG, electrocardiogram; ERT, extremely randomized tree; ICU, intensive care units; PPG, photoplethysmogram; RF, random forest; SVM, support vector machine.

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technical false alarms, and false alarms through interventions.² Clinical false alarms refer to the situation in which the physiological signal exceeds a preset threshold but is not clinically relevant. A default alarm setting in physiologic monitors may not appropriately reflect the individual patient's baseline or change in condition. For instance, a slow heart rate below 60 triggers an alarm which may be normal physiologically for some individuals or associated with an effective pharmacologic response.¹³ These high/low heart rate limits should be individually programmed as the same thresholds may not be appropriate for patients in cardiac ICU and those in medical ICU. Thus, customization of alarm settings based on individualized patient status can reduce the number of clinical false alarms and make the alarm more relevant to patient care.¹⁴ Graham and Cevach reported that providing nurses training about monitoring systems and regular assessment and individualization of alarm parameters can reduce false critical physiologic monitor alarms.¹⁵ Ruppel *et al.* also pointed out that customizing alarm settings enhances alarms' clinical relevance; however, alarm customization is a complex process, and little is known about the challenges nurses face when customizing alarms.¹⁴ In a mixed-methods study, Ruppel *et al.* reported variation in nurses' customization practices and confidence, unit-specific differences in alarm customization, and nurses were frustrated when they could not figure out how to customize specific arrhythmia alarms.¹⁴

Technical false alarms refer to the situation corresponding to a variable unrelated to surpassing the preset thresholds. Examples of these technical false alarms include a false asystole crisis alarm due to a low QRS amplitude and motion artifacts. The artifacts had an unfavorable effect on the physiologic waveforms that reduced the signal-to-noise ratio, leading to technical false alarms. Cho *et al.* found that 45.1% of the patient monitor alarms are false because of technical issues.¹⁶ Takla *et al.* reviewed extensive sources of common artifacts that affect physiologic monitor data,¹⁷ including movement artifacts (*e.g.*, patient movement and surgical preparation) or sensor artifacts (*e.g.*, circuit malfunction and losing contact). The detection and filtering of these artifacts can minimize technical false alarms.¹⁷⁻²⁰

Interventions to manage alarms can be a technological implementation within the monitoring system.²¹ Intelligent alarm algorithms, including machine learning, have attracted full attention for false alarm suppression in the ICU owing to their ability to discover unknown but ponderable information from a massive amount of medical data.²²⁻²⁶ Promising machine learning algorithms can overcome the challenges caused by irregular and high-dimensional ICU data.²⁷ These algorithms allow the integration of data from different sources and the incorporation of background knowledge in the analysis.²⁸ The renowned critical care databases, such as MIMIC-II²⁹ and ANZICS APD,³⁰ offer a wealth of data for machine learning models to learn features and mine the hidden information in the data. Progress has been made in algorithm development and improvement to identify false alarms generated by physiologic monitors and to discriminate feature patterns between alarms due to true patient instability or artifacts.¹⁹

The purpose of this review is to synthesize two main human-technology approaches to reduce false alarms generated by the physiologic monitor: customization of alarm settings by nurses and alarm algorithms.

Materials and methods

Data sources and search strategy

This review was performed according to the Guidance for conduct-

ing systematic scoping reviews.³¹ A broad search was performed for reports on the reduction of false alarms from physiologic monitors in ICU using two electronic databases, PubMed and Scopus. The following keywords were used alone or in combination to conduct this search: "ICU", "false alarm", "reduction", "critical care", "nurses", "nursing", "customization", "alarm fatigue", "machine learning", "deep learning" and the search was limited to articles published in English. All articles with publication dates ranging from database establishment to December 2020 were included. Another search was carried out to include non-duplicated articles from the EMBASE and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases. To identify further eligible studies, reference lists of the retrieved articles were also examined.

Inclusion and exclusion criteria

All studies that reduced the false alarms from physiologic monitors in ICU and employed participants or biomedical databases were considered eligible for our study. Specifically, eligible studies that met the following inclusion criteria were included: (1) clinical setting - ICU; (2) outcomes - reduction, causes, or consequences of the false alarms in the ICU, and (3) original research articles - reports of studies written by the researchers performed the studies. Studies were excluded according to the following exclusion criteria: (1) studies duplicated earlier publications, (2) studies were not related to false alarms in the ICU setting, (3) outcomes were not related to false alarms causes or reduction, (4) studies contained overlapping methods/algorithm, and (5) meta-analyses or systematic reviews.

Data extraction and appraisal

Two reviewers (JYH and SFW) extracted the following data from eligible studies: author name, publication year, study subjects, sample size, study design, interventions, and outcomes. The reviewers screened articles to ensure the studies met the inclusion criteria. A third reviewer (AL) was consulted in case of disagreement. The studies were appraised from two perspectives in terms of false alarm reduction: customization of alarm settings and alarm algorithm improvement.

Results

Literature selection and characteristics of eligible studies

Figure 1 illustrates a flowchart of literature search and selection. A total of 907 articles were initially identified through the literature search. Of these articles, 419 were from PubMed, 344 from Scopus, 120 from Embase, and 24 from CINAHL. Among these, 176 duplicate articles were removed. After the title and abstract of the remaining articles were screened, 604 additional articles were removed because they were not related to false alarm reduction in the ICU setting. After a full-text review, 99 reports were further excluded. These include reports not involving alarms in the ICU ($n = 34$), outcomes not related to false alarm causes or reduction ($n = 40$), articles with overlapping algorithms ($n = 22$), and reviews ($n = 3$). Finally, a total of 28 studies were included in this scoping review. The characteristics of the studies included in this review are presented in Tables 1 and 2.^{3,12,14-16,19,20,22-25,32-48}

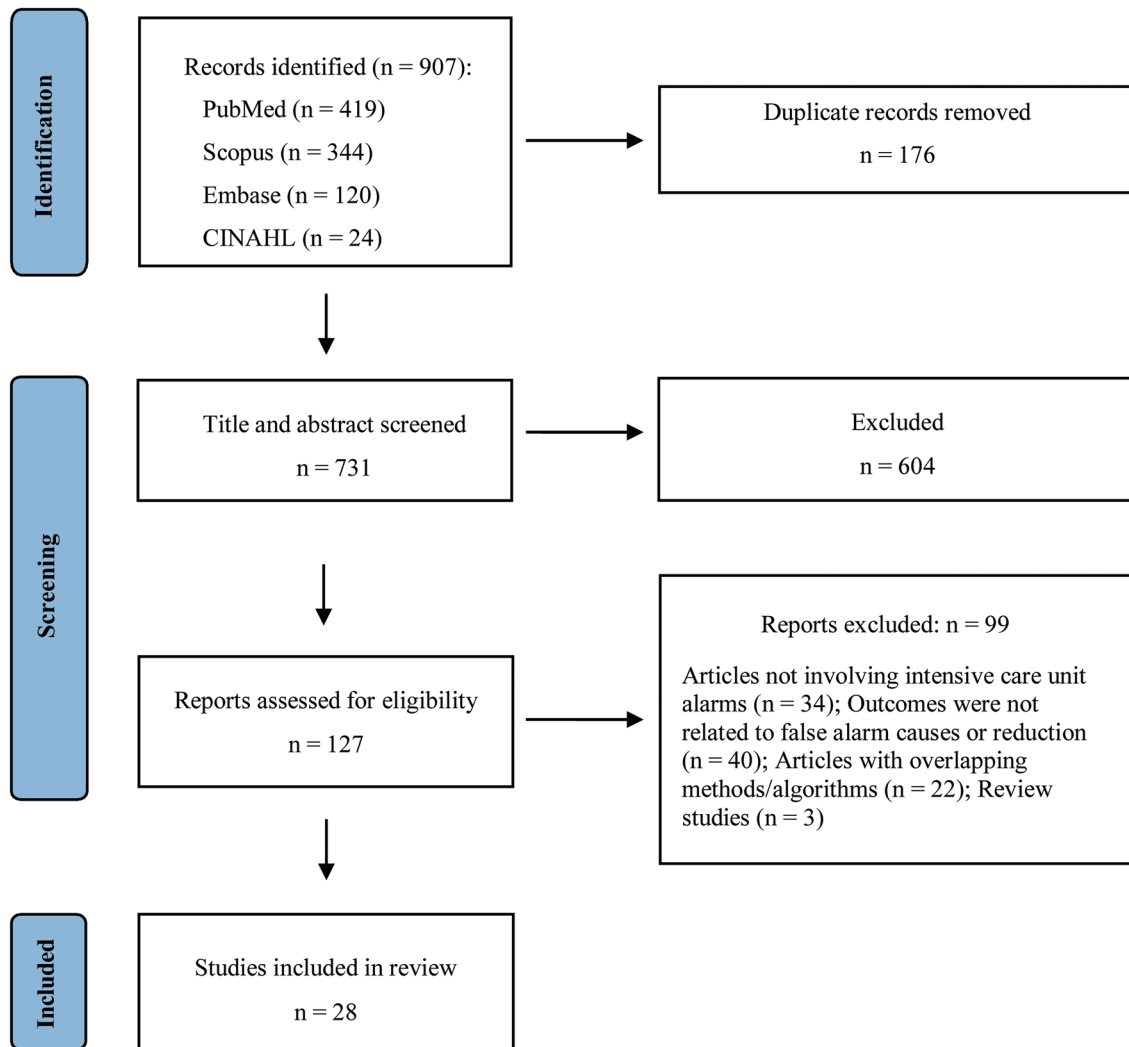


Fig. 1. Flowchart of literature search and study selection for this review.

Customization of alarm settings

Customization of alarm settings refers to adjusting the alarm settings based on each patient’s condition to minimize the irrelevant alarms without missing essential events. Graham *et al.*¹⁵ conducted a quality improvement project in which the nurses were trained to customize alarm parameters based on each patient’s needs and troubleshoot common monitor problems. Results showed that the number of high priority alarms decreased by 43% (from 16,953 to 9,647) in 18 days, suggesting customizing alarm settings can significantly decrease the number of alarms. In a randomized control study, Bi *et al.* conducted a 12-week alarm management training that significantly decreased the number of total alarms and non-actionable alarms ($p < 0.001$).³² However, in a Korean study, Cho and colleagues found that nurses only set personalized alarm ranges that reflected the patient’s conditions in only 18.8% of cases.¹⁶ The underlying reasons for many nurses in practice failing to set individualized alarm ranges for patients should be further studied.

It should be noted that the process of alarm customization involves clinical reasoning and decision-making. Some studies have examined which factors play an important role in this process.

Ruppel *et al.*¹⁴ found that a nurse’s clinical reasoning was affected by clinical expertise, lack of customization education, and negative experiences. A conceptual model was established to reveal the features that affect the customization of alarm and decision making.³³ Allan *et al.*³⁴ reported a bundled set of alarm reduction strategies, including alarm customization, reduced 61% of average alarms per monitored bed. Wung *et al.*³⁵ reported that nurses’ responses to the alarms were influenced by the type of alarm, workload status, and training on alarm devices. Multiple interacting factors may influence nurses’ alarm customization practice, however, clinical supports, such as education, structural training, and unit culture and policies, are of great importance to alarm management.

Honan *et al.* mentioned that clinical alarm management is important but not a panacea.³⁶ Evidence indicates that threshold customization is not enough to result in a significant reduction in alarm rates ($p = 0.57$).³⁷ Threshold adjustments manually can be either too small or too late to reduce the false alarms. Lewis *et al.*³⁸ employed a nurse-driven tool, the Communication, Electrodes, Appropriateness, and Setup alarm parameters, and Education (CEASE) bundle, and reduced 30% of the total number of monitoring alarms. This nurse-driven patient-customized monitoring bundle not only decreased the

Table 1. Customization of alarm settings

Study	Participant	Study Design/Intervention	Outcome
Graham <i>et al.</i> ¹⁵	30 nurses in a 15-bed care unit	Nurses were trained on the customization of alarm settings for individual patients.	Critical monitor alarms were reduced by 43% from baseline.
Ruppel <i>et al.</i> ¹⁴	ECG alarm customization of 298 patients in 3 ICUs and 27 nurses' customization clinical reasoning was explored	Conducted semi-structured interviews to explore the nurses' customization of clinical reasoning	58.7% of patients had alarms customized and factors that affect customizations were revealed.
Wung <i>et al.</i> ³	ICU nurses	Data analysis through a structured interview	Identified alarms from physiological monitors that contribute most to sensory overload.
Cho <i>et al.</i> ¹⁶	ICU nurses and devices from 48 critically ill patient cases	Data analysis through observation of alarms in 48 hours	Nurses personally set an alarm range that reflected the patients' condition in no more than 9 cases (18.8%).
Ruppel <i>et al.</i> ³³	27 ICU nurses	Thematic analysis of semi-structured interviews	Established a conceptual model to reveal the features affecting the customization of alarm.
Wung <i>et al.</i> ³⁵	16 ICU nurses	Analysis of decision-making process via semi-structure interviews	Identified the factors that nurses considered when deciding the response to an alarm in ICU
Honan <i>et al.</i> ³⁶	406 nurses' comments on perceptions of clinical alarms	Comments analysis using the Krippendorff method	Bedside nurses should set limits appropriate to the individual patient. Improved technology that recognizes trends in values to decrease nuisance alarms.
Fidler <i>et al.</i> ³⁷	77-bed from 5 ICUs	Quantitative analysis of heart rate alarms	Heart rate parameter adjustment did not lead to a reduction in alarms ($p = 0.57$).
Lewis <i>et al.</i> ³⁸	36-bed ICU/SDU	CEASE Bundle	The number of auditory monitor alarms decreased by 30.45% without adverse patient events.
Bi <i>et al.</i> ³²	93 ICU clinical nurses	The experimental group (n = 47) received alarm management training	The number of total alarms and nonactionable alarms from the physiological monitor decreased significantly in the experimental group ($p < .001$).
Allan <i>et al.</i> ³⁴	18-bed cardiac and vascular surgery ICU	Tested a bundle set of published practices, including education to staff regarding alarm customization, to reduce monitor alarm	A bundle set of alarm reduction strategies decreased the average alarms per monitored bed by 61%.

CEASE, Communication, Electrodes, Appropriateness, and Setup alarm parameters, and Education; ECG, electrocardiogram; ICU, Intensive care unit.

total number of monitoring alarms but also improved nurse perception of alarm fatigue.

Alarm algorithms for false alarm reduction

Artifacts in physiological signals, as a common source of the false alarm, have significantly lowered the patient care quality and safety in the ICU.⁶ Statistical and machine learning algorithms are common approaches to detect artifacts.² The algorithms to detect artifacts can be improved from three aspects: signal acquisition, validation of alarms, and alarm generation.¹

Several statistical approaches have been employed to improve signal extraction, such as median filters,³⁹ multivariate statistical methods, and signal quality assessment methods.^{40–42} These statistical manners are widely applied to reduce the artifacts.

The alarm fatigue can also be alleviated by reasoning the alarm generation and validation. Fernandes *et al.*¹² proposed a reasoning algorithm to group a set of alarms. The results showed that up to

99.3% (582/586) of total alarms were reduced without compromising patient safety.

In the past two decades, machine learning has raised the ever-increasing interest in classifying alarm events owing to its compatibility with complex data contexts.¹⁸ Machine learning combines statistics and computer science which uses input data to perform a task without being explicitly programmed (*i.e.*, “hardcoded”).⁴⁹ The parameters/architecture of the model can automatically alter based on observed data. Machine learning can deal with high dimensional data with multiple features as well as complex data formats, such as images, waveforms, etc. There are two types of classification algorithms in machine learning, linear and non-linear. The linear classifiers have the advantage of fast processing speed and the prerequisite is that data can be separated by a hyperplane. The non-linear classifiers, such as support vector machine (SVM) with Gaussian kernel function, random forest, and deep learning, have a higher tolerance to the noise and better performance. In this review, the term “machine learning” refers to traditional machine learning algorithms, including SVM, logistic regression, discrimi-

Table 2. Algorithms for false alarm reduction

Study	Data	Algorithm	Method	Outcome
Mäkivirta <i>et al.</i> ³⁹	Patients' data from a multi-parameter monitor	Statistical	Median filter	The true alarms rate increased from 12% to 49% without missing correct alarms.
Zong <i>et al.</i> ⁴⁰	PhysioNet's MIMIC	Statistical	Arterial blood pressure waveform quality combined with PPG waveform	Developed an algorithm that can suppress 100% of false ECG arrhythmia alarms based on the dataset.
Li <i>et al.</i> ⁴¹	MIMIC II	Statistical	Signal quality indices fusion and Kalman filter	An accurate heart rate estimate was achieved in the presence of persistent noise and artifacts.
Zong <i>et al.</i> ⁴²	MIMIC	Statistical	Signal quality assessment and fuzzy logic	98.2% (159/162) of false arterial blood pressure alarms were rejected while accepting 99.8% (441/442) of true alarms.
Fernandes <i>et al.</i> ¹²	Monitoring data and vital signs during surgical cases	Statistical	Automatic reasoning system	The reasoning algorithm filtered and reduced the notifications without compromising patient safety.
Pimentel <i>et al.</i> ⁴⁵	PhysioNet Challenge 2014	Machine Learning	Hidden Markov model and signal quality index	The overall score of the algorithm for the third phase of Physionet Challenge 2014 reached 83.47%.
Hravnak <i>et al.</i> ¹⁹	8-week vital sign data collected in surgical-trauma stepdown-unit	Machine Learning	Logistic regression for feature selection and multiple machine learning algorithms were employed for classification	The testing set achieved AUC scores of 0.94 respiratory rate, 0.84 blood pressure, and 0.72 SpO ₂ .
Lameski <i>et al.</i> ²²	MIMIC II	Machine Learning	RF, SVM, and ERT	The ERT suppressed over 90% of the TACHY false alarms with a low true alarm suppression rate.
Au-Yeung <i>et al.</i> ²³	PhysioNet Challenge 2015	Machine Learning	RF	Achieved a score of 83.08 in the real-time category on the hidden test set.
Li <i>et al.</i> ²⁴	MIMIC II	Machine Learning	Signal quality index assessment and relevance vector machine	False alarm suppression results were 86.4% for asystole, 100% for extreme bradycardia, and 27.8% for extreme tachycardia without suppressing true alarm
Eerikainen <i>et al.</i> ²⁵	PhysioNet Challenge 2015	Machine Learning	Signal pair selection and RF	The algorithm achieved a 93% true positive and 83% true negative rate in classifying cardiac arrhythmia alarms.
Srivastava <i>et al.</i> ⁴³	PhysioNet Challenge 2015	Machine Learning	RF and threshold approach assembling	The overall model performance reached an accuracy of 83.96%.
Krasteva <i>et al.</i> ⁴⁴	PhysioNet Challenge 2015, AHA, EDB, SVDB, MIT-BIH	Machine Learning	Signal quality and Decision tree	The algorithm achieved an overall real-time score of 80%.
Antink <i>et al.</i> ⁴⁶	PhysioNet Challenge 2015	Machine Learning	Binary classification trees, Discriminant analysis classifier, SVM	The algorithm achieved an overall real-time score of 75.55%.
Silva <i>et al.</i> ⁴⁷	MIT-BIH, CYBHI	Deep Learning	CNN	The positive prediction of R-peak was enhanced compared to the Pan-Tompkins algorithm in both databases.
Mousavi <i>et al.</i> ⁴⁸	PhysioNet Challenge 2015	Deep Learning	CNN with a two-step BP training	The algorithm achieved a sensitivity of 93.88% and specificity of 92.05% when considering three different signals.
Hooman <i>et al.</i> ²⁰	PhysioNet Challenge 2015	Deep Learning	CNN and DFO	The proposed method for training NNs improves the performance of detecting false alarms in ICU compared to backpropagation-trained networks.

AHA, American Heart Association Ventricular Arrhythmia Database; AUC, Area under the curve; BP, Back-Propagation; CNN, Convolutional Neural Network; DFO, Dispersive Files Optimization; ECG, Electrocardiogram; EDB, European ST-T Database; ERT, Extremely Randomized Tree; ICU, Intensive Care Units; MIT-BIH, MIT-BIH Arrhythmia Database; MIMIC, Medical Information Mart for Intensive Care; PPG, Photoplethysmogram; RF, Random Forest; SVDB, MIT-BIH Supraventricular Arrhythmia Database; SVM, Support Vector Machine.

nant analysis classifier, and other tree-based classification algorithms (random forest [RF] and extremely randomized tree [ERT]).

In the PhysioNet/Computing in Cardiology challenge 2105, several novel approaches integrated with machine learning have been proposed for the classification of false and true alarms.⁵⁰ Erikainen *et al.*²⁵ processed three physiological signals to confirm arrhythmias by choosing most matching signals pairs based on F1-score. Then specific arrhythmia features were calculated with customized windows varying from 14–16 seconds, followed by the classification through a random forest model. Srivastava *et al.*⁴³ ensembled random forests with a threshold approach. Random forest was implemented first for combinations of features extracted from electrocardiogram (ECG), arterial blood pressure, and photoplethysmogram (PPG), followed by a threshold set for parameters based on pulsatile waveforms. Krasteva *et al.*⁴⁴ employed a decision tree and introduced ECG quality to increase the signal-to-noise ratio. Then, a short scan interval of 3 to 7.5 seconds made it possible to give immediate feedback on arrhythmia events. Pimentel *et al.*⁴⁵ used the hidden Markov model and signal quality index to detect a heartbeat. Signal quality makes a significant difference in the classification of the alarm, even though it is not directly related to the arrhythmia characteristics.²³ The algorithm proposed by Antink *et al.*⁴⁶ involved multiple types of classifiers. Different classifiers were trained for specific arrhythmia alarms as well as a global classifier for general false alarms detection.

Deep learning, as a subfield of machine learning, has drawn increased attention to detecting or suppressing false alarms in the ICU. Deep learning structures algorithms in multiple layers to create an artificial neural network that mimics human brain structure and can learn from data and make decisions on its own. Deep neural networks can estimate much more complicated decision boundaries due to non-linear combinations of layers, thus, they can benefit from large amounts of data while the performances of traditional machine learning models plateau concerning increasing data size.⁵¹

Silva *et al.*⁴⁷ proposed a real-time approach based on convolutional neural networks (CNN) to enhance the positive prediction of heartbeat identification compared to the Pan-Tompkins algorithm, even though there was a slight decrease in the sensitivity of true heartbeat identification. Mousavi *et al.*⁴⁸ trained the CNN by a two-step backpropagation (BP) algorithm and achieved a sensitivity of 93.88% and a specificity of 92.05% for false alarm classification. Instead of BP, Hooman *et al.*²⁰ improved the deep neural networks' performance in the detection of false alarms in the ICU by applying the dispersive files optimization (DFO) algorithm to find an optimal weight for the model.

Discussion

The high rate of false alarms caused by clinical or technical factors significantly burdens the nurse, resulting in alarm fatigue, and compromising patient care quality and safety. This review summarized customization of alarm settings and alarm algorithm improvement as two approaches for false alarm reduction in the ICU.

Default alarm settings are inappropriate to reflect an individual's condition change and not all signals that exceed the default threshold are clinically relevant. On the other hand, artifacts that have unfavorable impacts on physiologic waveforms or reduce signal-to-noise ratios can cause technical false alarms. Moreover, false monitor alarms can also arise from the interaction of technical and clinical factors. According to these causes of false alarms in ICU, customization of alarm settings and improved alarm al-

gorithms can be great potential solutions to lower false alarms in the ICU.

Customizing alarm settings based on individual conditions can be a promising solution for clinical false alarms. Several studies found adjusting the alarm settings based on each patient's condition can reduce false alarms.^{15,16,32} Colleagues also noted the importance of alarm customization involves clinical reasoning and decision making.^{14,33–35} Previous studies also found that human behaviors play a role in response to alarms.^{52,53} Experienced nurses can dynamically change their activities according to the received information.⁵³ A nurse-driven patient-customized monitoring bundle can further reduce false alarms and improve nurse perception of alarm fatigue.³⁸ Therefore, Factors that affect nurses' customization and alarm management suggest that education and good unit culture are essential.

Although customization of alarms can reduce false alarms, it is not adequate to resolve all false alarms in the ICU. Intelligent alarm algorithms can effectively reduce technical false alarms by using multi-dimensional data to train the model. In the past, statistical approaches were widely applied to reduce the artifacts in false alarm reduction.^{39–42} Colleagues also found that combining information from different sensors can increase the positive predictive value of alarms.⁵⁴ Recently, machine learning has raised ever-increasing interest in classifying alarm events from multiple physiological signals.^{25,43–46,50} In addition, in the recent five years, deep learning has drawn increased attention to detecting or suppressing false alarms in the ICU.^{20,50,51} These studies show that modern machine learning methods with sensor fusion can effectively reduce false alarms.

Limitations

It should be noted that this study has a few limitations. First, this review was restricted to English-language papers published in academic journals, which may result in language and publication bias. Second, most alarm customization studies were conducted in America which may affect the generalizability of findings to other countries. Finally, the majority of the studies utilized AI/statistical approaches to suppress a single type of false alarm. Further investigations applying different technical approaches for multiple types of false alarm reduction are necessary.

Future directions

Human-in-the-loop approaches have great potential to further reduce the false alarms in ICU as they may leverage both the machine learning model and nurse decision making. Ideally, according to the machine learning model output, nurses can implement decision-making via a user interface to tune the model in real-time. The collaboration between nurses and engineers to optimize personalized machine learning algorithms may provide an effective solution for this critical issue in the future. Intelligent algorithms can be developed to learn an individual's baseline and provide timely feedback on the appropriate thresholds to guide personalized monitoring.

Conclusions

Clinical customizations of alarm settings on bedside physiological monitors helps to reduce excessive false alarms. Developed alarm

algorithms to reduce false alarms in the ICU have achieved excellent performance in detecting and suppressing a single type of false alarm. Future collaboration between nurses and engineers to optimize personalized alarm algorithms has the greatest potential for false alarm reduction in the ICU.

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Study design: SFW, JR, AL; Performance of experiments: JYH, SFW, AL; Analysis, and interpretation of data: SFW, JYH, AL; Manuscript writing: JYH, SFW, JR, AL; Critical revision: JYH, SFW, JR, AL; Administration: SFW, AL. All authors have made a significant contribution to this study and have approved the final manuscript.

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