Heart rate variability for medical decision support systems: A review

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Abstract

Heart Rate Variability (HRV) is a good predictor of human health because the heart rhythm is modulated by a wide range of physiological processes. This statement embodies both challenges to and opportunities for HRV analysis. Opportunities arise from the wide-ranging applicability of HRV analysis for disease detection. The availability of modern high-quality sensors and the low data rate of heart rate signals make HRV easy to measure, communicate, store, and process. However, there are also significant obstacles that prevent a wider use of this technology. HRV signals are both nonstationary and nonlinear and, to the human eye, they appear noise-like. This makes them difficult to analyze and indeed the analysis findings are difficult to explain. Moreover, it is difficult to discriminate between the influences of different complex physiological processes on the HRV. These difficulties are compounded by the effects of aging and the presence of comorbidities. In this review, we have looked at scientific studies that have addressed these challenges with advanced signal processing and Artificial Intelligence (AI) methods.

Keywords: Heart rate variability, Artificial intelligence, Computer-aided diagnosis, Patient remote monitoring

1. Introduction

If the heart trembles, has little power and sinks, the disease is advancing (the Ebers Papyrus c. 1530 BC). The ancient Egyptians understood that the pulse, that emanates from the heart, underpins disease diagnosis and prognostication. The pulse became a quantifiable parameter when Herophilos (335–280 BC) succeeded in timing its rate against a water clock. Using mechanical timepieces, Hales measured beat-to-beat interval variations in the pulse rate [1, Page 12], which predates, by more than 200 years, modern Heart Rate Variability (HRV) derived from digitized Electrocardiogram (ECG) recordings [2]. Initially, HRV analysis was confined to linear methods, such as statistical measures and frequency domain features. However, these measures fail to capture the rich complexities of beat-to-beat variations. As our understanding of the heart as a nonlinear oscillator grew, concepts of nonlinearity and chaos emerged as robust HRV measures [3]. Both linear and nonlinear features

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equip us with a plethora of methods to represent the information extracted from heart rate signals. This opens up opportunities to create systems which detect and track diverse diseases by analyzing HRV for clinical applications in diverse diseases. The basic premise is that a disease will induce a specific pattern of feature values, and the task remains therefore to identify disease-specific signatures in the feature continuum. Automating this process creates computer-aided diagnosis systems that can potentially improve healthcare delivery.

Progress in computing power and algorithm development are potent drivers of advances in HRV analytic methodology. Feature engineering plays a central role in information extraction and representation. At its simplest, statistical tests like Student's t-test and Analysis Of Variance (ANOVA) [4] are used to steer feature selection, feature combination, and decision border setting for specific problems, but that process can be prone to error. Initially, researchers mitigated the problem by developing machine learning algorithms [5] to establish both the feature importance and decision borders. While providing some level of automation, machine learning still requires subjective design decisions related to feature specification and selection. Deep learning approaches circumvent this requirement through objective data-driven feature engineering that fully automates the process while preserving classification performance [6]. Both machine learning and deep learning algorithms require training and testing based on curated ECG heart rate data samples labeled by human annotators. The scarcity of quality datasets poses a challenge to the data-centric development and growth of existing and future HRV analysis systems. The choice of method crucially hinges on data access and size as deep learning demands significantly more training data than classical machine learning. Further, inherent data biases, as well as intra- and inter-observer variabilities, can dampen the discriminative utility of medical decision support models for clinical diagnosis, monitoring, and prognostication.

In this work, we aimed to conduct a systematic review of healthcare applications for HRV analysis systems, their methods and performance as well as the specific clinical domains. To this end, 713 scientific papers were screened and 130 were selected for in depth review. The selected papers were categorized into 15 different application areas: cardiology, mental health, sleep health, lifestyle, Intensive Care Unit (ICU) settings, blood pressure, remote monitoring, comorbid conditions, oncology, brain health, addiction, and drug abuse, diabetes, respiratory, epilepsy, and infant health. All studies incorporated Artificial Intelligence (AI), with newer studies espousing deep learning as opposed to older ones based on classical machine learning. With this review, we consolidate and in some specific areas extend existing knowledge on HRV analysis for medical decision support systems. The following list substantiates that claim:

- To the best of our knowledge this is the first review that focuses on HRV based medical decision support for automated healthcare systems.
- Our goal was to create a resource for researchers which encourages future work on HRV applications.
- We indicate the best machine learning techniques for specific application areas. That can be a starting point for new investigations, and it can provide a frame of reference that can be used during the assessment of new results.
- Similarly, we indicate the best deep learning methods for specific application areas.
- We highlight shortcomings of current HRV based medical decision support and propose possible solutions.
- We have also discussed future directions of advanced HRV based healthcare systems. Outlining the future directions went beyond just addressing current shortcomings.

The remainder of the manuscript is structured as follows. In Section 2, the background to heart rate physiology and measurement techniques is explained. Our search methodology is detailed in Section 3; and findings are presented and discussed in Sections 4 and 5 respectively. Section 6 concludes our review.

2. Background

Under normal circumstances, the cardiac sinoatrial node controls the heart rhythm. That process takes input from both the parasympathetic and sympathetic divisions of the autonomic nervous system [7]. In response to that input, the heart rhythm can be modulated over a wide frequency band [8]. The aim of regulating the heart rhythm is to maintain homeostasis and thereby stabilize the internal physiological state [9]. That effort can be observed by recording the beat-to-beat interval of the human heart and HRV analysis allows us to extract information which can be used as biomarkers and for medical decision support.

The way in which we acquire and analyze beat-to-beat variability is shaped by measurement technology and signal processing methods. The text below describes two measurement methods followed by a discussion on the analysis of beat-to-beat interval variations.

2.1. Electrocardiography

Electrodes are placed on the skin of the chest wall and limbs to record over time the surface electrical potentials that emanate from cyclical electrical signal conduction between muscle tissues of the various heart chambers. Analogue ECG potentials are sampled and quantized to digital sample streams. Typical sampling frequency and quantization resolution are 250 Hz and 12 bits, respectively, which yield an ECG data rate of 3000 bits/s. This modest data rate, coupled with the non-invasive ECG recording setup, render ECG acquisition highly accessible in both ambulatory and hospital settings.

2.2. Photoplethysmography

Photoplethysmogram (PPG) signals depict blood volume fluctuations in a superficial body location and reflect pulsatile blood pressure changes during each heart cycle. The signals can be measured with low-cost optical sensors placed on the skin of an area with sufficient circulation, e.g., fingertip. Beat-to-beat intervals can be extracted from PPG using software algorithms. Ease of sensor placement, its non-invasive nature, and low-cost render PPG feasible for heart rate measurements. The peak amplitudes of the PPG signal may become attenuated by hemodynamic perturbations, e.g., impaired perfusion from systemic hypotension or local blood vessel blockage, which impairs the detection. Also, the optical sensor may lose contact with the skin, resulting in signal loss and reduced monitoring efficacy.

2.3. Beat-to-beat interval

The QRS complex on the ECG represents the start of heart muscle depolarization; and the time duration from one R wave peak to the next R wave peak constitutes the beat-to-beat interval (RR interval) or time elapsed between two consecutive heartbeats. The latter can be recorded as a simple one-dimensional vector where each entry represents an ECG RR interval. Similarly, the time duration from one peak of the blood volume curve to the next peak on the PPG signal represents the beat-to-beat interval. RR interval signals have an average data rate of about 12 bits/s. That data rate is significantly lower when compared to typical ECG data rate. That makes RR interval signals more suited for bandwidth critical applications, such as wireless sensing and data transfer over digital mobile networks [10, 11]. The quality of the medical decision support system provided by a classification algorithm is crucially dependent on the fidelity of beat-to-beat interval detection. In general, the PPG signal peak is less pronounced compared with the ECG R wave, which may

Table 1: Boolean search strings

Database	[Title]	AND [Full text and Metadata]	No. of studies
PubMed	Heart Rate Variability, RR interval	"Machine Learning" "Artificial intelligence" "Deep learning" "Neural Network"	98
Google Scholar		"Machine Learning" "Artificial intelligence" "Deep learning" "Neural Network" "Prediction"	258
IEEE		"Machine Learning" "Artificial intelligence" "Deep learning" "Neural Network"	254
Science Direct		"Machine Learning" "Artificial intelligence" "Deep learning" "Neural Network"	103

undermine detection accuracy and render it more susceptible to noise. On the other hand, it may be difficult to discern the QRS complex consistently from other ECG waves, e.g., prominent P and T waves, in certain pathologies, resulting in inaccurate beat-to-beat interval determination.

Medical decision support based on HRV analysis operates in the landscape created by medical need, technological capability, and health economics. It is important to know both the individual application area and the wider trends in HRV analysis to construct a credible argument for specific medical decision support systems. The next section introduces the individual application areas for HRV analysis, and the technology used for medical decision support. Together with the objective review results, presented in Section 4, that might provide both depth and breadth needed to make commercial as well as research decisions.

3. Article search and selection methods

We performed a systematic search of all entries in four databases within the period between 2010 and 2021. These databases were: ScienceDirect, PubMed, IEEE Xplore, and Google Scholar. Pre-specified Boolean search strings (Table 1) were used to query the databases. We chose this period because lots of forward-looking work on AI has been done during that time, which is not surprising due to increasing computing power, a critical mass of talent, and the snowballing impact of innovations. Through the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method, we excluded duplicate items, review articles, conference papers, non-English publications, Master's research, works unrelated to AI, and manuscripts without Accuracy (ACC) results (Figure 1).

3.1. Article analysis

From an in-depth review of the 130 eligible articles (Figure 1), we identified 15 distinct application areas and broad technical categories. This led to a review framework for scientific studies on HRV based healthcare systems.

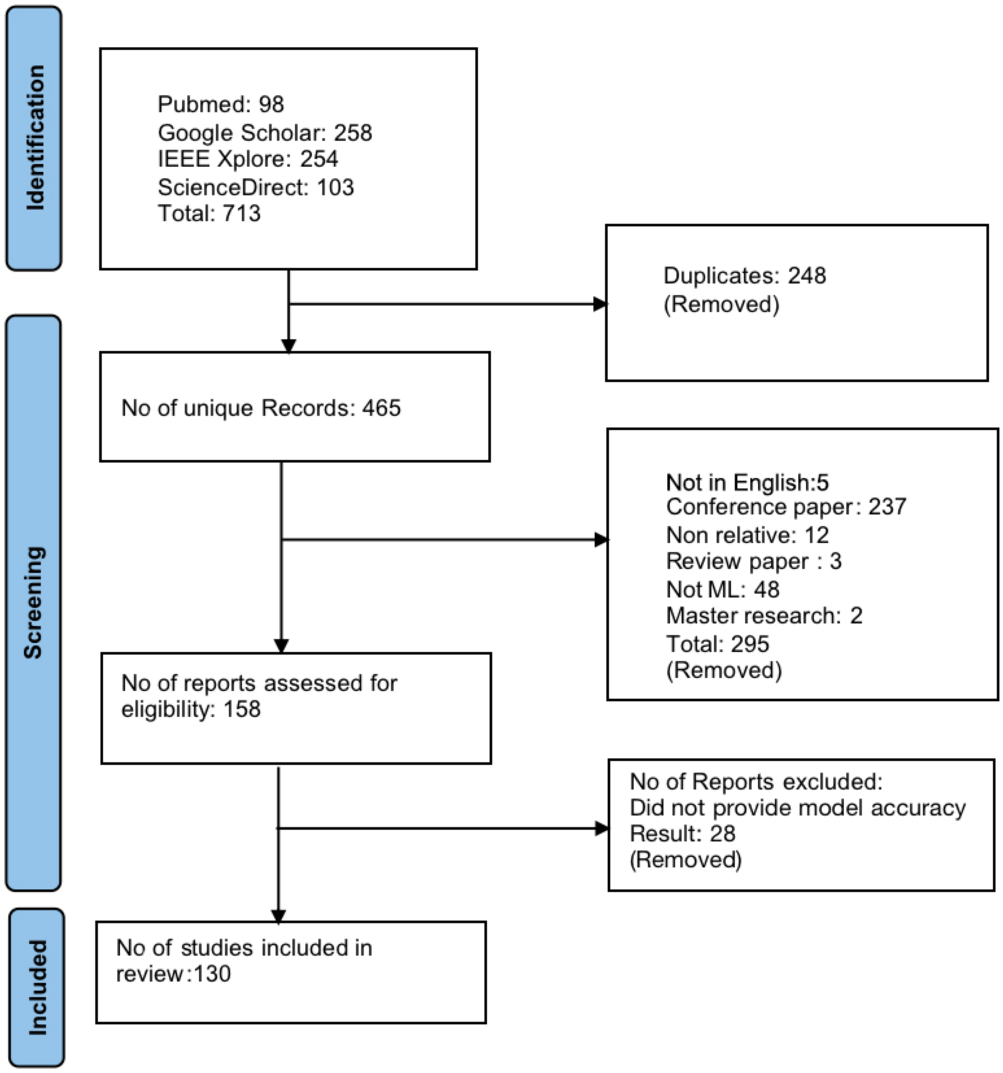

Figure 1: Flow chart of the PRISMA model for article selection.

3.2. Application areas

Automated HRV analysis can enable medical decision support systems for a wide range of application areas. These systems address specific medical needs by providing objective information derived from the beat-to-beat variability of the heart. To be specific, application area-specific AI models extract objective information and this information is put to use in medical decision support systems.

To select appropriate application areas, we balanced intra-group commonality with inter-group distinctiveness, and also limited the variance resulting from the number of papers mapped to a specific application area.

3.2.1. Cardiology

Unsurprisingly, cardiology attracted most studies on HRV analysis as diverse cardiological conditions are known to exert strong influences on the heart rhythm [12, 13]. As such, cardiology is a diverse field with numerous specialisations. To reflect this diversity, we have introduced nine subcategories. These subcategories were: congestive heart failure, atrial fibrillation, cardiovascular, arrhythmia, heart failure, ventricular tachyarrhythmia, sudden cardiac death, cardiomyopathy, various cardiac pathologies ventricular fibrillation.

3.2.2. Mental Health

Different mental health conditions can induce changes in HRV due to crosstalk between the central nervous and cardiovascular systems that are mediated by the autonomic nervous system [14]. To tease out the HRV signature pattern, associated with specific mental disorders, is challenging due to the diverse clinical presentations that may evolve. To address that challenge will require large datasets and longitudinal studies with long follow-ups. On the positive side, ECG-based HRV analysis for mental health is more expedient and cheaper than Electroencephalogram (EEG), which makes it more accessible, including for ambulatory and longer duration data acquisition. These important advantages have motivated researchers to work in this application area.

3.2.3. Sleep Health

Closely linked to mental health, sleep health can similarly be assessed via sleep EEG recordings in specialized laboratories, which is the reference standard. The inconvenience and high cost limit its use, which may incentivize the use of HRV-based diagnosis. While heart rhythm is physiologically linked to sleep-related brain processes through the autonomic nervous system, it is difficult to recognize sleep-related HRV changes because sleep is a highly individualized activity with high diversity in observable signal patterns. Despite these difficulties, we found 15 publications that addressed sleep health by providing medical decision support based on HRV analysis. The majority of work (seven studies) focused on sleep apnea detection. As such, sleep apnea is a condition where a patient stops and starts breathing during sleep. The absence of oxygen supply to the body is likely to trigger perturbations that cause the autonomic nervous system to regulate the HRV [15].

3.2.4. Lifestyle

HRV is a physiological indicator of human health and fitness [16], although the link is vaguely defined with ample scope for interpretation. In general, lifestyle interventions pose low or minimal risk and there can be little or no ethical objection to implement physiological monitoring to guide the choice and dose of beneficial lifestyle intervention, e.g., type and intensity of exercise training. Unlike conventional medical care, lifestyle applications are generally unregulated and the use of adjunctive HRV monitoring becomes a personal choice based on individual perception of cost and benefits.

3.2.5. Intensive care unit settings

Continuous heart rate monitoring is routine in ICUs. While instantaneous pulse rates may dictate the need for emergency action, automated HRV analysis of pulse data acquired over a longer time window offers an additional dimension that may be more useful for contextualizing future or imminent risks to critical cases in intensive care [17, 18].

3.2.6. Blood Pressure

High blood pressure typically develops over years and a patient may be largely asymptomatic. Early detection is important for lifestyle changes and long-term medication to be effective in averting complications. Blood pressure is in part controlled by, and some anti-hypertensive drugs target the autonomic nervous system. Accordingly, HRV analysis may be used alongside blood pressure measurements for early detection and management of diseases, such as central hypovolemia [19], hypertension [20, 21].

3.2.7. Monitoring

The low data rate of single-channel ECG facilitates remote wireless cloud-based heart rate monitoring and automatic real-time HRV analysis [22]. The use case is strengthened by the ability of HRV analysis to monitor a wide range of conditions, not all of which are mutually exclusive, e.g., it is possible to monitor sleep and detect atrial fibrillation concurrently.

3.2.8. Comorbid

The impact of a specific medical intervention is difficult to predict in a patient with comorbid conditions. Continuous real-time HRV analysis may be used to calibrate specific interventions in such patients to preempt hemodynamic perturbations [23, 24]. In general, the individual's comorbidity and the effect on HRV cannot be directly extrapolated from prior knowledge or other studies. As such, there needs to be a level of individualization established through trend analysis.

3.2.9. Oncology

While HRV analysis is not a primary cancer detection tool, it can play an important role during rehabilitation and in disease progression prediction [25, 26, 27]. For the former, continuous HRV analysis facilitates the monitoring of known complications, such as pain and stress. The latter is technically more challenging, and might involve multimodal approaches that fuse imaging with HRV analysis.

3.2.10. Brain

As mentioned, there is a strong link between the brain and heart mediated by the autonomic nervous system. While not a primary diagnosis tool for organic brain diseases and injuries, HRV analysis can provide additional accessible real-time information for disease progression monitoring, therapeutic response, and prognostication.

3.2.11. Addiction and Drug Abuse

Substance abuse can impact the autonomous nervous system profoundly [28, 29]. HRV analysis may unveil the effects of addictive behavior on heart health. In a rehabilitation setting, HRV analysis may be used for progress tracking and outcome assessment.

3.2.12. Diabetes

Diabetes neuropathy can directly impair the autonomic nervous system, which blunts HRV [30]. In addition, treatment-induced hypoglycemia may stimulate the sympathetic nervous system [31]. As such, HRV analysis can be used to monitor the physiological state of diabetes. Further, HRV analysis may be helpful for monitoring salutary lifestyle intervention (Section 3.2.4) in diabetes.

3.2.13. Respiratory

The cardiovascular and respiratory systems are vital for ensuring adequate perfusion of oxygenated blood to all organs in the body, and pathophysiology in either system often exert collateral influence on the other as well [32, 33]. While it is not a primary diagnostic tool for respiratory disease, HRV analysis can be useful for tracking the severity of respiratory disease involvement longitudinally.

3.2.14. Epilepsy

EEG is the reference standard for establishing epilepsy diagnosis and monitoring treatment response. However, data acquisition requires onerous instrumentation, and a training phase to tune the signal processing algorithms to the measurement setup might be necessary. Further, it is not possible to perform EEG on a continuous ambulatory basis. Due to the heart-brain connection mediated by the autonomic nervous system, HRV may manifest subtle changes in the presence of or even before epileptic seizure even though it may not be pathognomonic in itself [34, 35]. HRV's low-cost, convenience, and capability for prolonged remote may observation hold the key to its application as a long-term surveillance monitor in the suspected epileptic patient for predicting rather than diagnosing seizure episodes.

3.2.15. Infants

Due to the ease of setup, the use of HRV as a physiologic monitor in infants, who have limited ability to vocalize symptoms, holds promise for applications in baby care and pediatric critical care [36, 37]. In the former, remote continuous HRV monitoring showing results within physiological limits will give parents psychological peace of mind. In the latter, real-time HRV analysis can be used to support the constant monitoring of vulnerable infants.

3.3. Medical decision support

Medical decision support can improve healthcare processes by providing objective information about individual patients and it can be used to shift the analytic work from humans to computers. This has cost and reliability advantages as computer-based algorithms are scalable and not subject to intra- and inter-observer variability. Conceptually, HRV-based medical decision support can be delivered in three ways (Figure 2). First, features extracted from heart rate signals can be used directly for tracking the health of a patient. Pulse rate is an example of such a feature which is an important component of established early warning scores [38]. Second, the extracted feature or multiple features can be combined with machine learning algorithms. By increasing the information input, multiple features can enhance the decision quality. The machine learning algorithm discovers feature weight (importance) and decision borders that, once established, allows the model to efficiently label fresh unseen heart rate signal samples for medical decision support. Third, deep learning can perform automatic labeling of heart rate signal samples without explicit feature engineering. That opens up a direct and independent information pathway for decision support from the patient to the physician. The following subsections provide details of the individual medical decision support methods.

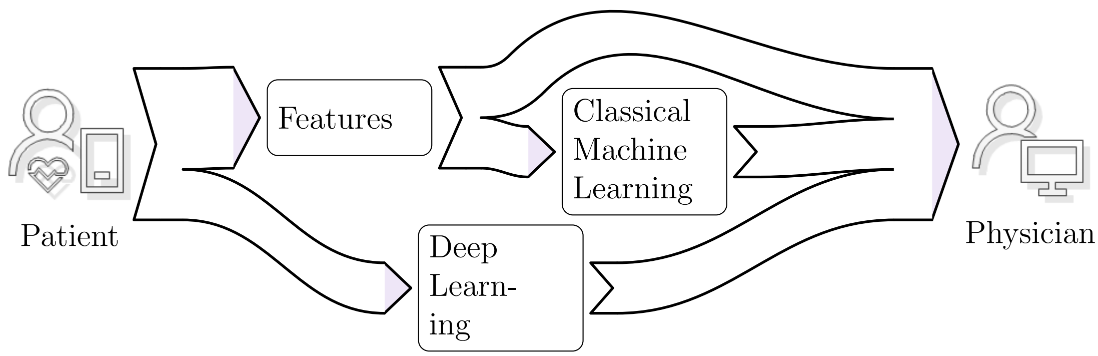

Figure 2: Information pathways for medical decision support.

3.3.1. Feature engineering and classical machine learning

Feature engineering demands a deep understanding of the problem and expert knowledge of information extraction methods [39]. The human designer has to decide on which features to extract as well as the selection criteria, these processes are usually guided by statistical feature analysis. The selected features are then fed into a machine classification algorithm to train the medical decision support model using samples that have been previously labeled by experts. Once trained and validated, machine classification algorithms can be used to establish specific inference results, e.g., detecting a specific disease, without the need for fresh medical experts to track multiple features.

Selecting the machine classification algorithm is a subjective activity. To address that issue, most authors train and test a range of methods and, once all performance results are established, select the algorithm which optimally addresses the problem. The following machine classifiers were used to provide medical decision support based on HRV features: Support Vector Machine (SVM), Multilayer Perceptron (MLP), Classification And Regression Tree (CART), Extreme Learning Machine (ELM), Logistic Regression (LR), Recurrent Neural Network (RTF), Artificial Neural Network (ANN), Random Forest (RF), Gradient Boosting (GB), Decision Tree (DT), K-Nearest Neighbor (KNN), Probabilistic Neural Network (PNN), AdaBoost, Gaussian Process Classification (GPC), Partial Least Squares Discriminant Analysis (PLS-DA), Statistical Classifier (SC), Auto-regressive Moving Average with Exogenous Inputs (ARMAX), Adaptive Network-based Fuzzy Inference System (ANFIS), Linear Discriminant Analysis (LDA), Autoencoder (AE).

3.3.2. Deep learning

Deep learning incorporates feature engineering as part of the algorithm. Features are automatically adjusted to optimize the classification results. Compared with machine learning, deep learning requires larger amounts of data samples, the model quality improves as the number of data samples increases. Where there is insufficient labeled data, deep learning algorithms risk overfitting, i.e., learning from the data itself rather than the knowledge contained in the data. Among many different options, two deep learning model classes have been widely used for HRV analysis: Convolutional Neural Network (CNN) and Recurrent Neural Network (RNN).

CNN has been designed to mimic the human visual perception system and was originally purposed for two-dimensional data in application domains, such as medical image analysis. Due to good performance, CNN can be adapted to analyze one-dimensional signals like HRV in two distinct ways. First, the HRV signal is transformed into a two-dimensional image to input to the CNN. The second approach is to use a CNN subclass to process the signals before they are fed to the fully connected layers of the CNN for classification. The main drawback of using CNN for HRV analysis is that the input images contain only spatial but not temporal information. The temporal aspect of HRV analysis is patently important because disease symptoms may not be present all the time and even if present, may induce nonlinear rhythm variations that can only be detected with good knowledge about the temporal unfolding of the signals. RNN can overcome the shortcoming of CNN. The main structural difference between RNN and CNN is that RNN incorporates internal feedback loops that generate an infinite impulse response, whereas CNN is only capable of producing a finite impulse response [40]. Systems with an infinite impulse response are more sensitive to temporal changes in a signal. This effect is augmented when the memory, within the algorithm, is controlled via learned parameters, such as in the widely used Long Short-Term Memory (LSTM) networks.

4. Results

From 2010 to October 2021, there has been a firm increase in the number of published papers that meet our search criteria, described in Section 3, with 40 articles being published in 2021 alone (Figure 3). Analyzing the information pathways used by the reviewed studies reveals that deep learning methods were introduced in 2018. Since then, the number of articles on that topic is steadily increasing. Figure 4 shows the 130 studies on HRV analysis mapped onto the 15 application areas introduced in Section 3.2. The average number of papers in each application area is 8.67 ± 12.61. The large standard deviation of 12.61 indicates a strong concentration of papers for certain application areas. Indeed, cardiology and mental health were the subjects for more than 50% of the reviewed papers. Figure 5 shows the mapping of reviewed papers onto the cardiology sub-categories. The mapping reveals that HRV analysis is most often used for arrhythmia detection. This was expected because the main symptom of arrhythmia is abnormal heart rhythm. For mental health, the number of published articles was also mapped onto subcategories (Figure 6): 6 mental illness, 4 stress, 3 emotion, 3 driver's mental state (a safety-related concern with wider social and commercial implications), 2 cognitive tasks, 1 emotional eating, and 1 music.

Among the reviewed papers, there were 21 AI (18 machine learning and 3 deep learning) algorithms that were used in common for medical decision support (Figure 7). The bar graph in Figure 8 shows that machine learning with SVM is the most popular with 31 studies in total. The deep

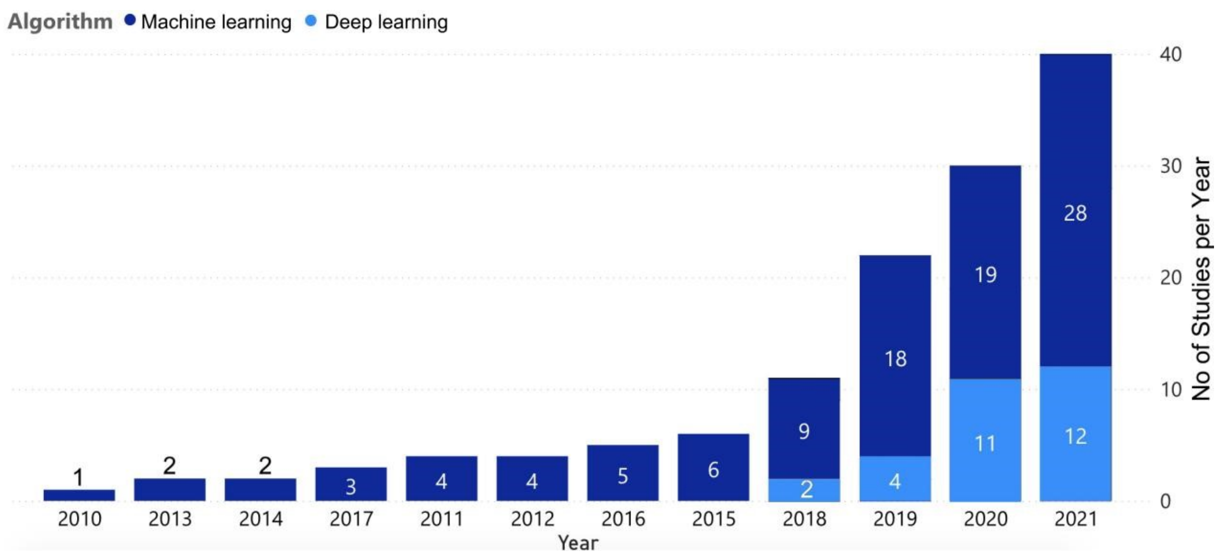

Figure 3: Number of HRV studies within one year over a time period from 2010 to 2021.

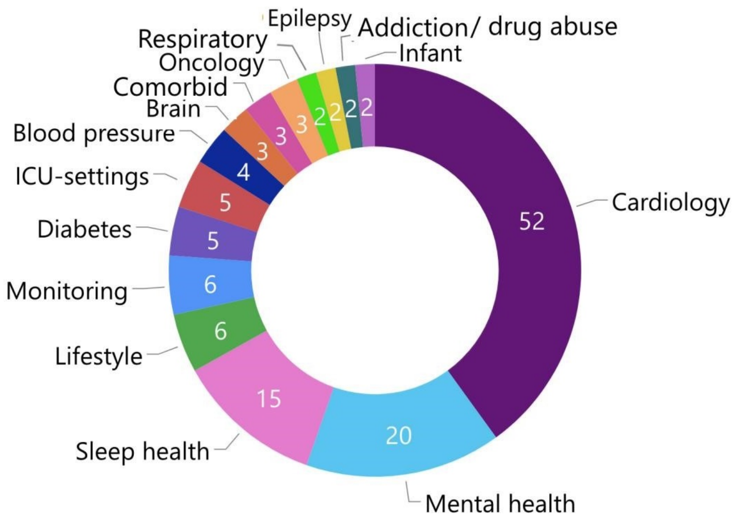

Figure 4: Mapping studies to application areas.

learning methods CNN and RNN were used 6 and 5 times, respectively. Details of individual study methods and accuracy rates are provided in Tables A.2 to A.16.

The radar plot in Figure 9 indicates that RF yields the highest ACC when compared to all other machine learning algorithms. The graph also indicates that all discovered machine learning algorithms yield an ACC of over 90%.

The radar plot in Figure 10 indicates that CNN achieves the highest ACC when compared to RNN and hybrid. Indeed, the classification accuracy stayed above 99.4% for the considered deep learning methods.

Figure 11 shows the maximum ACC achieved for each of the application areas. Oncology studies achieved the highest ACC score. However, that result might not reflect a general trend, because the statistic was based on only three oncological studies. In comparison, cardiology applications show excellent accuracy with small variance in a large number of studies (52), which lends support to the use of HRV analysis for decision support in this clinical domain. The lowest mean accuracy and highest variance are seen in the addiction/drug abuse and mental health areas, respectively. This suggests that more confirmatory studies are needed before HRV analysis can be used for medical decision support in these application areas.

The radar diagram shown in Figure 5 details the max ACC for the cardiology subcategories.

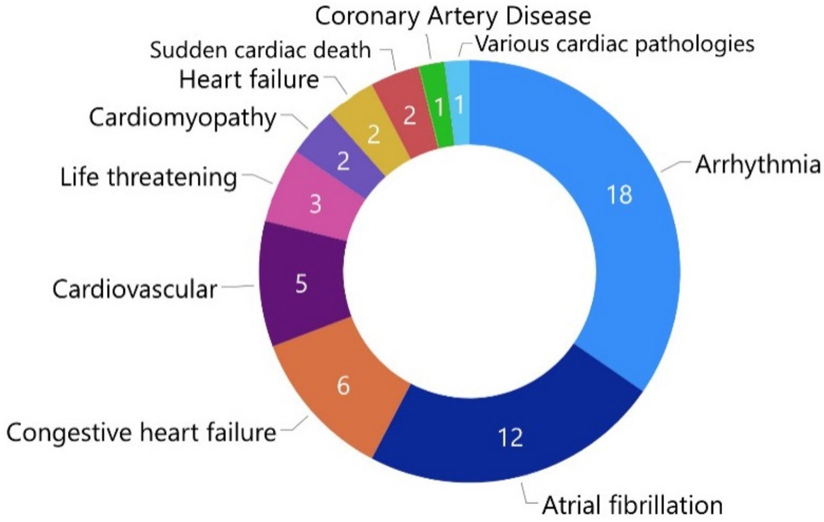

Figure 5: Distribution of studies for the cardiology sub-categories.

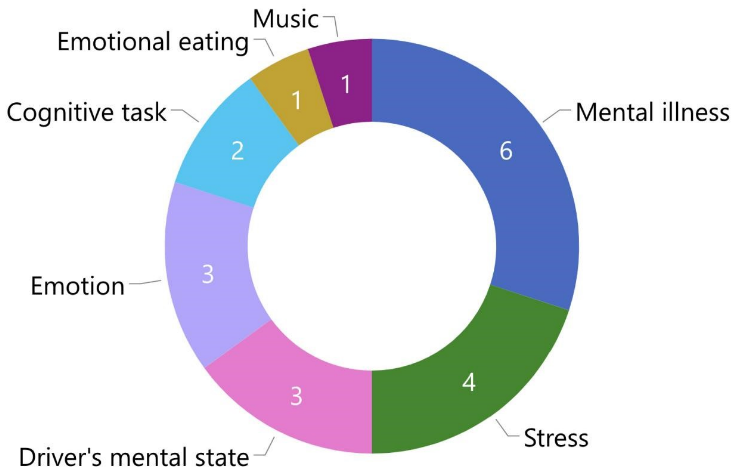

Figure 6: Distribution of studies for the mental health sub-categories.

The radar diagram shown in Figure 13 details the max ACC for the mental health subcategories.

5. Discussion

In this review, we have surveyed the contemporary knowledge base on HRV analysis and its application in the medical domain. Development in HRV analysis is deeply intertwined with technological progress. Current measurement technology support is in a mature state of development whereas computational advances in signal analysis, through feature engineering, are accelerating. Modern computing technology allows us to use the accrued knowledge to create systems that automate analysis tasks to provide decision support more efficiently and accurately.

Traditional machine learning methods facilitate the tracking of multiple features to provide objective decision support [6]. Since 2018, there is a shift from machine to deep learning that is driven by the need for more transferable knowledge and the availability of more training data. All the reviewed papers share a vision about a future where automatic HRV analysis can play an important role for disease detection, which is enabled by medical decision support systems that can mimic expert human knowledge. The next step will be to create systems that can learn data patterns before a

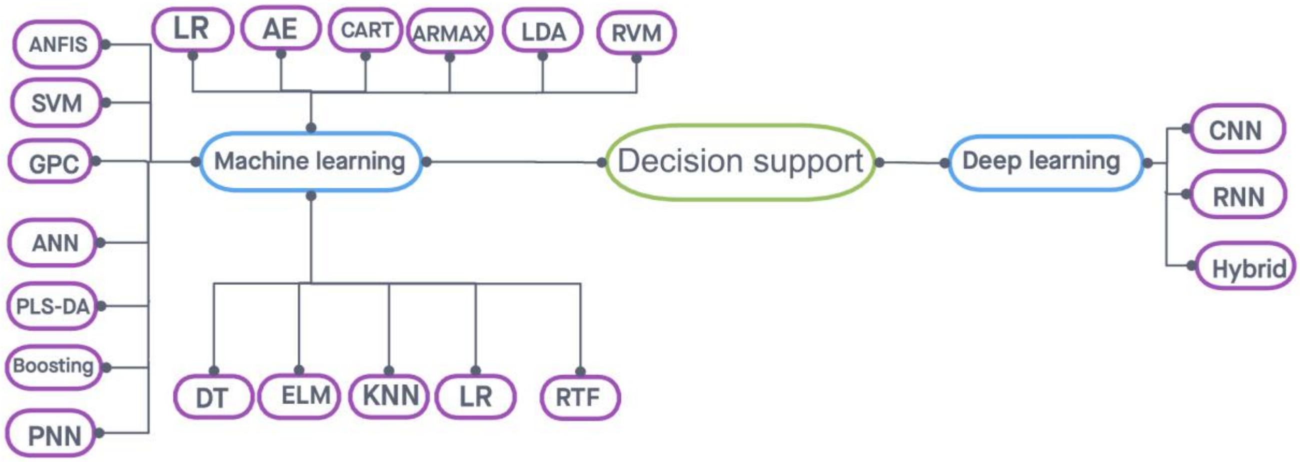

Figure 7: Mindmap of medical decision support algorithms.

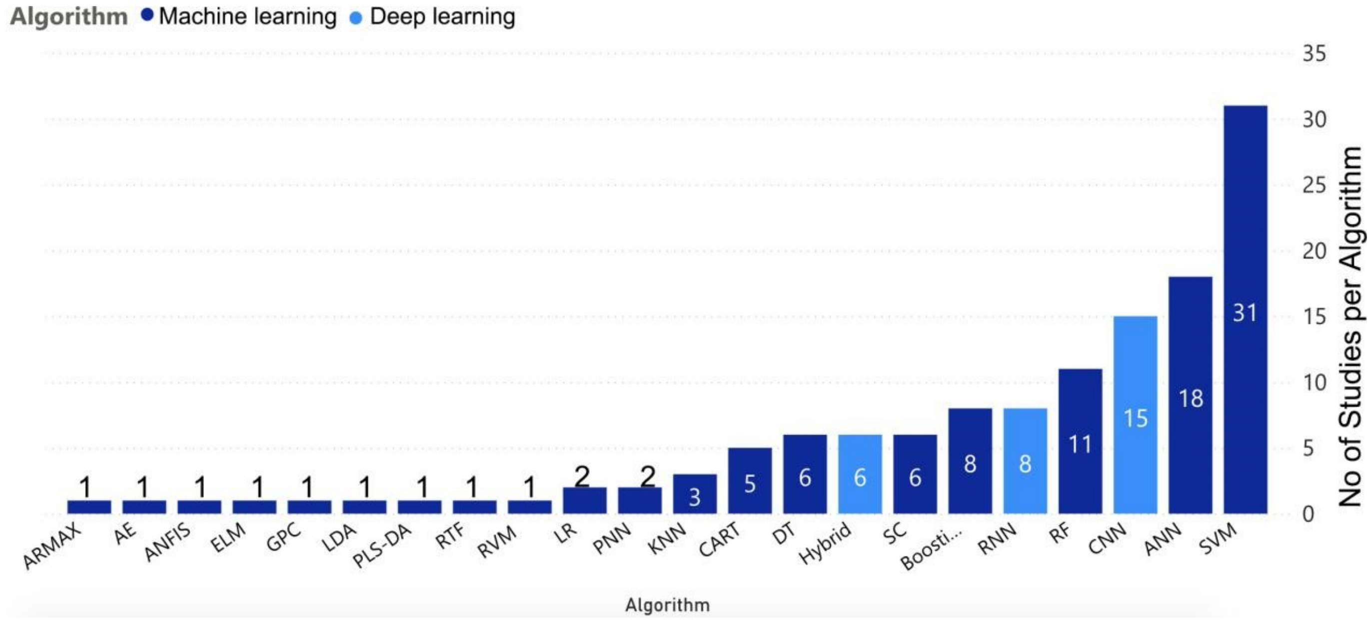

Figure 8: Number of specific medical decision support algorithms found in the reviewed studies.

disease develops, allowing us to transit from diagnosis support to disease prediction. Many disease-induced HRV changes may be subtle and are devoid of symptoms. The ability to predict diseases has significant clinical impact because early detection and indeed disease prediction will reduce the need for invasive intervention. In the best case, all the interventions that will be needed are beneficial lifestyle changes that can improve outcomes in patients.

With our expert review framework, we established that cardiology is by far the most prevalent application area of HRV analysis. This is hardly surprising given the fact that HRV describes the beat-to-beat interval of the human heart which is correlated to the pumping of the heart. Mental health and sleep health are the second and third most often researched application areas. As such, this was not immediately expected, because HRV is a secondary measure for these conditions [14]. However, these application areas benefit from the fact that it is possible to use HRV instead of EEG, which has both cost and patient comfort benefits. The same holds true for the epilepsy application area and to some extent for addiction / drug abuse. For sleep apnea, which is defined as stop and start breathing during sleep, the respiratory application area overlaps with sleep health [15]. But there

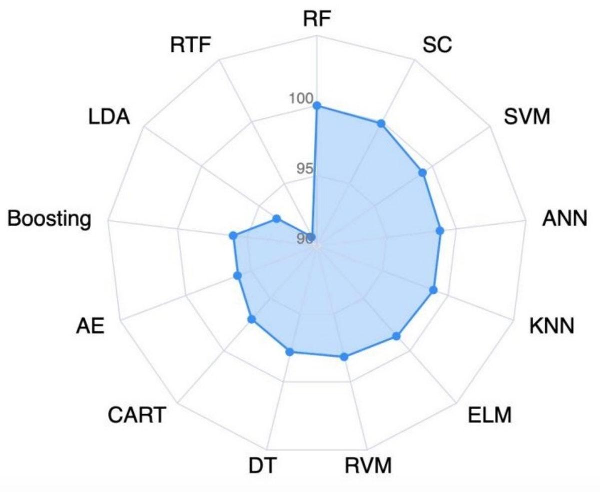

Figure 9: Maximum ACC of classical machine learning models across all application areas.

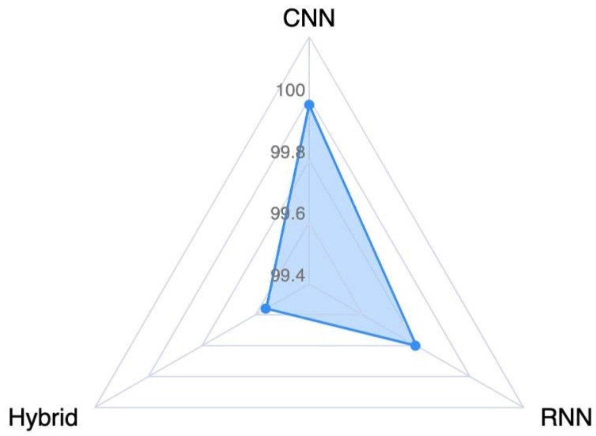

Figure 10: Maximum ACC of deep learning models across all application areas.

are respiratory related application areas outside sleep. Lifestyle, which is the fourth most researched application area, might be supported by the most advanced and holistic healthcare philosophy [41]. Suggesting lifestyle choices is the least invasive form of intervention, therefore a patient stands to gain the most from such support. However, suggesting lifestyle choices in an end-of-life situation is clearly nonsense, therefore even lifestyle choice support is not universally applicable. In most cases, end-of-life considerations concern older patients with multiple conditions and diseases. In such a situation, HRV analysis can offer objective healthcare support [42]. To be specific, in a comorbid situation the focus widens from an individual disease to the general health of a patient. An intervention for a specific disease might have side effects that make other conditions worse which results in negative outcomes for patients. HRV analysis can play a positive role in providing a holistic health assessment. Moving to the opposite side of the age spectrum by discussing the infant application area reveals an important property of HRV analysis. Namely, the beat-to-beat variations are age-related [43]. Hence, it is necessary to train and test medical decision support algorithms with infant data for that application area.

HRV analysis is likely to play an important role when it comes to extending the remit of ICU care. This extension is accomplished in terms of both location and time. Extending ICU care to more locations is a cost factor and HRV analysis together with automated medical decision support might be a way of accomplishing a higher level of care with the same resources. The second point about extending ICU care over time is an attempt to improve ICU care itself. Monitoring a patient over time allows us to establish a trend that can be instrumental when it comes to intervention decisions

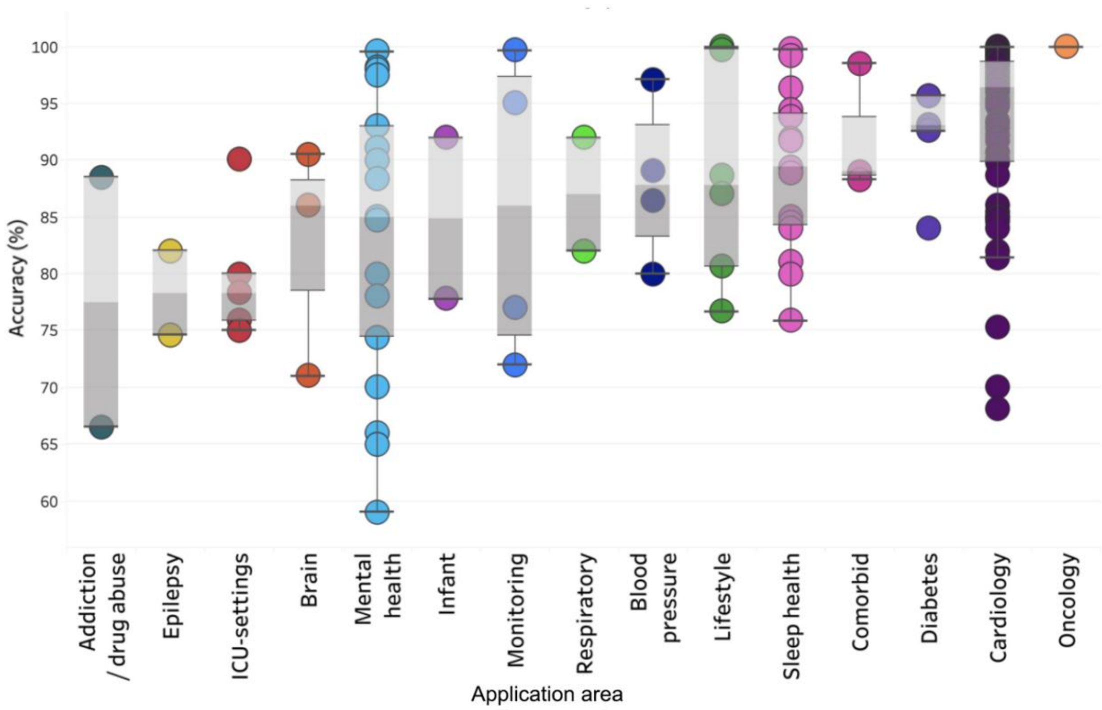

Figure 11: Box plot of achieved accuracy for the individual application areas.

[17, 18]. Indeed, this is where extending ICU care in time becomes intertwined with extending it in terms of location. For example, it might be possible to monitor heart rate in an ambulance and through wireless and cloud technology establish the patient condition which can be monitored at the hospital. From a more abstract perspective, it is the low data rate that makes heart rate signals very easy to communicate, process, and store. In this case, very easy implies cost and convenience benefits. These are certainly the drivers behind the monitoring application area.

Having three studies dedicated to diabetes detection indicates that there is a strong link between this disease and HRV analysis [30]. This link is less pronounced for oncology applications, which is expressed by the relatively small number of studies that were dedicated to that application area. Similarly, for the brain application area, the number of studies found was also only three, which indicates that it is difficult to exploit the link between brain processes and HRV.

Each application area has specific limitations. The reviewed scientific studies contribute by proposing application area-specific decision support. Thereby, they overcome or at least reduce some of the specific limitations. These individual improvements have the potential to create progress for the entire field of HRV analysis. However, general limitations exist, and addressing them might require a concerted effort. The next section introduces these general limitations.

5.1. Limitations

HRV reflects the health of a person, hence having a normal heart rate signal implies perfect health. As the body ages, this becomes harder to achieve because some physiological processes might operate outside normal parameters, due to impending age-related diseases. The task for computer-aided diagnosis systems is to determine the cause of the HRV changes and thereby provide medically relevant information. The situation gets even more complex when more than one condition is present. In such comorbid cases, the HRV changes caused by one disease might overshadow the changes caused by another. Even if this is not the case, there is currently limited knowledge on how to discriminate the HRV changes from two or more diseases.

The transition from classical machine learning to deep learning has profound technical and ethical implications. The absence of feature engineering allows deep learning methods to extract more

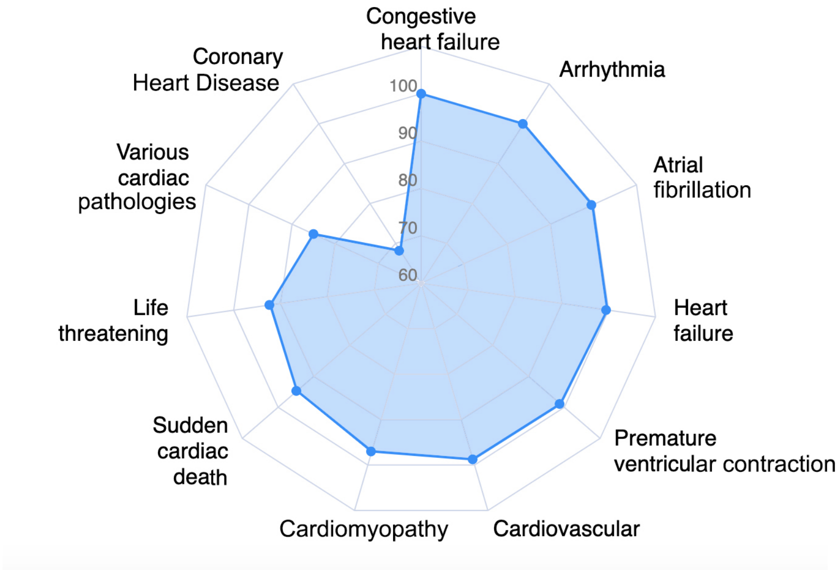

Figure 12: Medical decision support algorithm and maximum accuracy achieved for cardiology sub-categories.

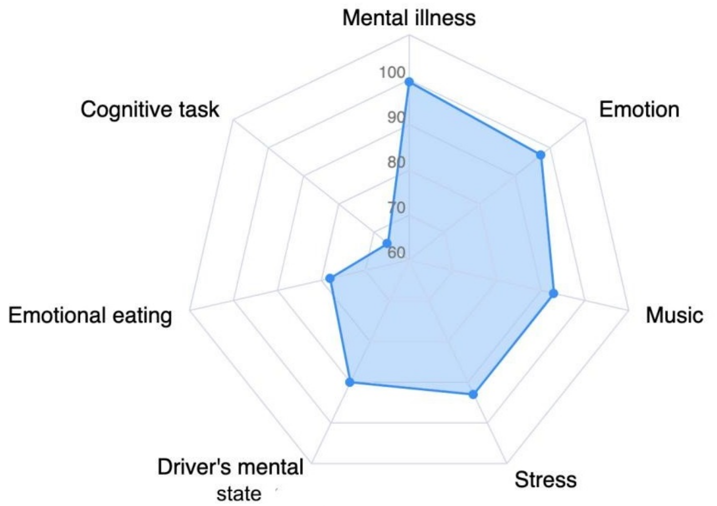

Figure 13: Maximum accuracy achieved for the mental health sub-categories.

transferable knowledge from a given dataset. However, machine learning techniques are more explainable when compared to deep learning techniques. The lack of explainability implies that the decision might not make sense to a human observer. This creates an ethical problem, especially for medical applications because diagnosis support systems should be accountable for the provided service. Traditionally, accountability is established through the explainability of actions. Following that logic, less explainability leads to less accountability. This is a considerable hurdle to the future development of deep learning models, notwithstanding the burgeoning research interest and good classification performance.

There are several barriers when it comes to building learning HRV analysis systems. During the design phase, it is difficult to assess the progress of a learning system. Currently, AI systems are assessed by comparing disease detection results from an AI algorithm with the detection results from human experts, which is not always perfect. So long as human diagnosis remains the reference standard, AI cannot transcend the limits of human knowledge and expertise in medical decision support systems.

Another limitation for learning systems arises from the practicalities of working with big data. Our working hypothesis is that there exist patterns in the HRV signals from a large number of patients that can reveal insights into disease development, disease risk stratification, and disease prediction. In truth, the emergence of a specific pattern in big data is likely chaotic, implying a threshold, say the number of patients, where a specific pattern is not visible. This is an additional unknown that renders specific study setups vague and unclear. In short, such studies will encounter difficulties to explain what they are looking for and where they are looking for it. Therefore, we envision that learning systems will emerge as a side product of working with large quantities of heart rate data. As an analogy, the closest systems that are currently implemented are customer profiling algorithms from social media companies. The customer-facing application enables these companies to accrue learning systems for customer analysis. If this notion that big data analytics is a side product that is best enabled by another fronting application is accurate, this will pose a significant barrier to big data research on HRV. Namely, the availability, processability, and real-time nature of the data. Companies and institutions that collect large volumes of heart rate data are most likely not willing to share or are constrained from sharing these data. Hence, actively designing learning systems might only be possible in a commercial setting with explicit consumer consent on the terms of use, including commercialization, which is not always possible in the healthcare setting.

5.2. Future work

Future work should go beyond merely addressing the limitations of current systems with refinement of technologies or methods. We must build a bridge that leads into a future where heart rate is routinely measured in an unobtrusive way convenient for patients and healthy people alike. We believe that data gathered from heart rate measurements can benefit a wide range of individuals. Indeed, we predict that pervasive use of physiological measurements, chief among them heart rate capturing, will blur the distinctions of what it means to be healthy and diseased, with actionable thresholds for preventive interventions along the feature continuum.

In our review, we have identified 15 application areas where HRV analysis can help to address specific medical needs. Looking beyond the individual areas and indeed beyond the individual problem solutions, we recognize that the signal acquisition step is common to all these applications. The algorithms, incorporated for medical decision support, are distinct for individual application areas. Having common and distinct functionalities are the hallmarks of product and indeed service platforms. In the future, such platforms will allow us to repurpose common functionalities, especially those that establish signal acquisition, communication, and storage, for new and innovative services at scale. By offering multiple services with a common infrastructure, we can exploit the economies of scale to bring down the cost of individual services. We envision that there will be low-hanging fruits with proven clinical value, such as ambulatory detection of atrial fibrillation detection, that will help to solidify the base of the common infrastructure. Once that infrastructure is in place and the number of users grows, there will be opportunities for more innovative service offerings to capitalize on the network effect where more users will spark more services, which in turn brings down the cost for the individual services, thus creating a virtuous cycle.

The service design principle might also unlock the problem of analyzing HRV from comorbid patients because it allows us to individualize the service functionality. Having cost-efficient signal acquisition, communication, storage, and processing allows us to monitor such patients over long-time durations. That means each patient has a heart health record that holds significant information for individualized health assessment and prognosis. Based on this individualized assessment it might be possible to optimize interventions that improve outcomes for comorbid patients.

Collecting large volumes of heart rate data with unobtrusive measurements opens up the opportunity to learn from data itself. Currently, our HRV-based medical decision support methods merely reflect the knowledge of human experts. To be specific, we train and test AI algorithms with data that have been labelled by human experts. In the future, it might be possible to mine knowledge from the data itself. This will automate the knowledge creation process. Automated knowledge creation might fill the gaps in our understanding of the relationship between HRV and the physiological processes that influence heart rhythm. Having such a holistic approach can potentially enhance the power of disease prediction and long-term prognostication.

6. Conclusion

HRV is a good predictor of human health. During our review, we found strong support for this statement. With a structured literature search, on the four most common scientific paper databases, we curated 130 manuscripts. These papers formed the basis of our expert review on HRV for healthcare systems. During this step, the main achievement was to identify 15 distinct application areas for HRV. Identifying both information pathways from the patient to the physician and decision support technologies used was a corollary activity. Having that understanding of application areas and the technologies used in the studies, enabled us to create a framework with which we could categorize the papers.

In this review, we show that HRV analysis continues to attract and indeed fascinate a wide range of researchers. This continued interest might be sparked by the fact that HRV analysis seems rather unpretentious and explainable – it reflects the pumping activity of the heart. However, as the research progresses boundaries of understanding emerge, and more knowledge is needed to cross them. Indeed, the need to create more knowledge is another significant driver for the continued interest in HRV for healthcare systems. This knowledge creation is intricately intertwined with technological progress. Our current understanding is that big data and AI algorithms will result in breakthroughs for HRV-based healthcare technology. Initially, these breakthroughs might be rather theoretical, but HRV analysis is a very practical topic and new knowledge will inevitably lead to new healthcare systems. This practicality results in part from the signal intelligibility and the low data but high information rate. It can be noted from this review, in the future there will be more studies using HRV as a base signal to improve the quality of life.

7. Acronyms

ACC Accuracy
AE Autoencoder
ANFIS Adaptive Network-based Fuzzy Inference System
ANN Artificial Neural Network
ANOVA Analysis Of Variance
AI Artificial Intelligence
ARMAX Auto-regressive Moving Average with Exogenous Inputs
CART Classification And Regression Tree
CNN Convolutional Neural Network
DT Decision Tree
ECG Electrocardiogram
EEG Electroencephalogram
ELM Extreme Learning Machine
GB Gradient Boosting
GPC Gaussian Process Classification
HRV Heart Rate Variability
ICU Intensive Care Unit
KNN K-Nearest Neighbor
LDA Linear Discriminant Analysis
LSTM Long Short-Term Memory
LR Logistic Regression
MLP Multilayer Perceptron
PLS-DA Partial Least Squares Discriminant Analysis
PNN Probabilistic Neural Network
PPG Photoplethysmogram
PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RF Random Forest
RNN Recurrent Neural Network
RTF Recurrent Neural Network
SC Statistical Classifier
SVM Support Vector Machine

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Appendix A. Mapping research studies onto application areas

Table A.2: Cardiology related studies.

Author, Year	Objective	Approach	Dataset	ACC (%)
Pecchia et al., 2010 [44]	Chronic heart failure detection	CART	83 subjects	96.40
Jovic et al., 2011 [45]	Patient type classification	RF	100 subjects	99.70
Joo et al., 2012 [46]	Ventricular tachyarrhythmia prediction	ANN	258 records	92.20
Mohebbi et al., 2012 [47]	Atrial fibrillation prediction	SVM	106 segments	92.86
Melillo et al., 2013 [48]	Congestive heart failure detection	CART	41 participants	85.40

Liu et al., 2014 [49]	Premature heartbeat detection	ANN	134 recordings	98.90
Poddar et al., 2015 [50]	Coronary artery disease detection	SVM	124 subjects	91.67
Fujita et al., 2016 [51]	Sudden cardiac death prediction	SVM	41 subjects	94.70
Raj et al., 2016 [52]	Arrhythmia detection	SVM	47 subjects	99.18
Faust et al., 2018 [53]	Atrial fibrillation detection	RNN	47 subjects	99.77
Singh et al., 2019 [54]	Arrhythmia detection	ANN	48 subjects	97.13
Jovic et al., 2019 [55]	Congestive heart failure detection	RTF	108 subjects	90.70
Hu et al., 2019 [56]	Congestive heart failure detection	SVM	83 subjects	96.70
Qu et al., 2019 [57]	Congestive heart failure detection	SVM	29 subjects	84.00
Kong et al., 2019 [58]	Atrial fibrillation detection	Probabilistic SVM	1960 subjects	98.16
Wang et al., 2019 [59]	Congestive heart failure detection	SC	156	99.85
Chen et al., 2019 [60]	Arrhythmia detection	Hybrid	47 subjects	96.62
Agliari et al., 2020 [61]	Cardiac pathology detection	ANN	2829 patients	85.00
Zhang et al., 2020 [62]	Cardiovascular disease prediction	Boosting	2111 subjects	75.30
Yan et al., 2020 [63]	Cardiovascular event prediction	Boosting	2442 subjects	81.40
Silveri et al., 2020 [64]	Dilated cardiomyopathy detection	CART	972 subjects	97.00
Shi et al., 2020 [65]	Beat classification	Hybrid	47 subjects	99.26
Taye et al., 2020 [66]	Ventricular tachyarrhythmia prediction	CNN	261 subjects	84.60
Sanjana et al., 2020 [67]	Tachycardia detection	RNN	8642 records	96.47
Romdhane et al., 2020 [68]	Deep learning method for arrhythmia detection	CNN	47 subjects	98.41
Chen et al., 2020 [69]	Arrhythmia detection	Hybrid	47 subjects	99.56
Rieg et al., 2020 [70]	Arrhythmia detection	DT	10,646 patients	95.35
Hirsch et al., 2020 [71]	Atrial fibrillation detection	RF	23 subjects	97.40

Martinez-Alamis et al., 2020 [72]	Sudden cardiac death risk prediction	SVM	91 patients	86.00
Sharma et al., 2020 [73]	Arrhythmia detection	RNN	47 subjects	90.07
Buscema et al., 2020 [74]	Atrial fibrillation detection	ANN	73 patients	95
Fujiwara et al., 2021 [75]	Extrasystole detection	AE	18 participants	96
Jeong et al., 2021 [76]	Ventricular fibrillation prediction	ANN	118 subjects	88.64
Silva-Filho et al., 2021 [77]	Myocardial infarction prediction	Boosting	218 subjects	96.00
Castro et al., 2021 [78]	Atrial fibrillation prediction	KNN	100 subjects	93.24
Alkhodari et al., 2021 [79]	Left ventricular ejection fraction level detection	RF	142 subjects	70.00
Selek et al., 2021 [80]	Congestive heart failure detection	RF	83 subjects	100.00
Parsi et al., 2021 [81]	Atrial fibrillation prediction	SVM	75 subjects	97.70
Saiz-Vivo et al., 2021 [82]	Atrial fibrillation detection	SVM	74 subjects	82.00
Mandal et al., 2021 [83]	Prediction of atrial fibrillation	SVM	25 patients	99.11
Gan et al., 2021 [84]	Arrhythmia detection	Hybrid	47 subjects	99.44
Faust et al., 2021 [85]	Arrhythmia detection	CNN	10,646 patients	98.37
Pandey et al., 2021 [86]	Heartbeat classification	Hybrid	48 recordings	98.58
Ivaturi et al., 2021 [87]	Atrial fibrillation detection	CNN	8,528 recordings	84.93
Wang et al., 2021 [88]	automatic ECG classification method	CNN	47 subjects	98.74
Li et al., 2021 [89]	Coronary heart disease detection	CNN	106 patients	68.15
Murawwat et al., 2021 [90]	Arrhythmia detection	ANN	7 subjects	89.80
Xu et al., 2021 [91]	Heartbeat classification	ELM	47 subjects	98.61
Keidar et al., 2021 [92]	Atrial fibrillation detection	DT	25 recordings	97.8
Lee et al., 2021 [93]	Smart scale	KNN	56 subjects	98.90
Faust et al., 2021 [94]	Arrhythmia detection	CNN	10,646 patients	99.98
Gupta et al., 2021 [95]	Burnout detection	SC	1615 participants	77.00

Dias et al., 2021 [96]	Arrhythmia detection	LDA	48 recordings	93.40

Table A.3: Addiction or Drug Abuse related studies.

Author, Year	Objective	Approach	Dataset	ACC (%)
Nayak. et al., 2020 [28]	Cannabis consumption effects analysis	Boosting	200 participants	66.50
Pop et al., 2021 [29]	Alcohol impact on the autonomic nervous system	Boosting	142 participants	88.50

Table A.4: Blood pressure related studies.

Author, Year	Objective	Approach	Dataset	ACC (%)
Tajera et al., 2011 [97]	Pregnancy type classification	ANN	217 participants	80.00
Ji et al., 2013 [19]	Hypovolemia detection	SVM	87 participants	89.10
Zhang et al., 2019 [20]	Hypertension prediction	RF	209 participants	86.44
Alkhodari et al., 2020 [21]	Hypersensitivity detection	Boosting	139 patients	97.08

Table A.5: Brain related studies.

Author, Year	Objective	Approach	Dataset	ACC (%)
Verde et al., 2019 [98]	Carotid disorder classification	ANN	126 participants	90.50
Megjhani et al., 2020 [99]	Neurocardiogenic injury detection	LR	382 participants	86.00
Odenstedt Hergès et al., 2021 [100]	Cerebral ischemia detection	RF	48 participants	71.00

Table A.16: Mental health related studies.

Author, Year	Objective	Approach	Dataset	ACC (%)
Patel, 2011 [136]	Driver fatigue detection	ANN	12 participants	90.00
Valenza et al., 2014 [137]	Depression characterisation	ANN	5 participants	99.56
Bilgin, 2015 [138]	Anxiety level detection	ANN	90 participants	91.11

Nardelli et al., 2015 [139]	Emotion recognition	SC	27 subjects	84.72
Liew et al., 2015 [140]	Stress detection	SC	22 subjects	80.00
Goshvapour et al., 2017 [141]	Emotion discrimination	PNN	47 participants	97.45
Peláez et al., 2018 [142]	Stress identification	DT	50 subjects	93.00
Posada-Quintero et al., 2019 [143]	Cognitive task identification	KNN	16 participants	66.00
Byun et al., 2019 [144]	Depression detection	SVM	78 subjects	74.40
Byun et al., 2019 [145]	Depressive detection	SVM	66 participants	70.00
Moridani et al., 2020 [146]	Stress classification	CNN	20 participants	98.00
Persson et al., 2020 [147]	Driver alertness detection	RF	86 subjects	85.00
Coutts, 2020 [148]	Stress level detection	RNN	1652 participants	85.00
Zontone et al., 2020 [149]	Driver stress detection	SVM	14 subjects	88.40
Juarascio et al., 2020 [150]	Emotional eating risk detection	SVM	21 participants	77.99
Frasch et al., 2021 [151]	Autism detection	Boosting	69 participants	59.00
Jin et al., 2021 [152]	Stress detection	CNN	56 participants	98.20
Chung, 2021 [153]	Emotion classification	PLS-DA	239 subjects	65.00
Borisov et al., 2021 [154]	Cognitive load classification	SC	23 participants	66.00
Idrobo-Ávila, 2021 [155]	Heart stimuli analysis	RF	26 subjects	93.00

Table A.6: Comorbid related studies.

Author, Year	Objective	Approach	Dataset	ACC (%)
Melillo et al., 2015 [23]	Cardiovascular and cerebrovascular event prediction	RF	139 patients	89.00
Shao et al., 2020 [24]	Cardiovascular and cerebrovascular event prediction	SVM	139 patients	88.31
Alkhodari et al., 2021 [101]	Neuropathy detection	CNN	100 subjects	98.50

Table A.7: Diabetes related studies.

Author, Year	Objective	Approach	Dataset	ACC (%)
Seyd et al., 2012 [102]	Diabetes detection	ANN	135 subjects	93.08
Pachori et al., 2016 [103]	Diabetes detection	SVM	30 participants	95.63
Swapna et al., 2018 [104]	Diabetes detection	SVM	20 subjects	95.70
Rathod et al., 2021 [105]	Diabetes detection	CART	213 subjects	84.04
Shashikant et al., 2021 [106]	Diabetes risk prediction	GPC	135 participants	92.59

Table A.8: Epilepsy related studies.

Author, Year	Objective	Approach	Dataset	ACC (%)
Sung et al., 2020 [34]	Seizures detection	SVM	20 patients	82.00
Fang et al., 2021 [35]	Vagus nerve stimulation outcome prediction	SVM	109 subjects	74.60

Table A.9: ICU-setting related studies.

Author, Year	Objective	Approach	Dataset	ACC (%)
Liu et al., 2011 [107]	Outcome prediction	SVM	100 subjects	78.32
Liu et al., 2015 [108]	Mortality prediction	LR	108 patients	80.00
Nagaraj et al., 2017 [109]	Sedation detection	SVM	70 subjects	75
Oh et al., 2018 [17]	Delirium detection	SVM	140 subjects	75.88
Zhan et al., 2021 [110]	Anaesthesia detection	ANN	23 patients	90.10

Table A.10: Infant related studies.

Author, Year	Objective	Approach	Dataset	ACC (%)
Lewicke et al., 2012 [36]	Cardiorespiratory event prediction	SVM	1079 subjects	77.80
Herry et al., 2021 [37]	Zika virus detection	SVM	21 subjects	92.00

Table A.11: Lifestyle related studies.

Author, Year	Objective	Approach	Dataset	ACC (%)
Chiu et al., 2016 [111]	Music selection	DT	30 subjects	76.67
Botsva et al., 2017 [112]	Predictors of aging	ANN	22,433 participants	87.00
Matta et al., 2018 [113]	Activity state detection	ANN	31 participants	88.70
Goshvarpour et al., 2018 [114]	Psychological state detection	PNN	23 subjects	100.00
Singh et al., 2018 [115]	Age detection	SVM	40 subjects	99.71
Mashhadimalek et al., 2019 [116]	Well-being level detection	DT	31 participants	80.64

Table A.12: Monitoring related studies.

Author, Year	Objective	Approach	Dataset	ACC (%)
Choi et al., 2011 [117]	Stress monitoring	ARMAX	4 subjects	72.00
Jaros et al., 2019 [118]	Fetal hypoxia detection	ANFIS	37 subjects	99.69
Boujnouni et al., 2019 [119]	HRV prediction	RNN	1 subject	-
Kim et al., 2019 [120]	Biometric authentication	DT	70 samples	95.00
Quintanar-Gómez et al., 2021 [121]	Blood pressure detection	ANN	-	-

Table A.13: Oncology related studies.

Author, Year	Objective	Approach	Dataset	ACC (%)
Shukla et al., 2018 [25]	Lung cancer prognosis	SVM	134 subjects	100.00
Shukla et al., 2018 [26]	Pulmonary metastases prognosis	SVM	54 subjects	100.00
Shukla, 2018 [27]	Lung cancer prognosis	SVM	134 subjects	100.00

Table A.14: Respiratory related studies.

Author, Year	Objective	Approach	Dataset	ACC (%)
Rahman, 2019 [32]	Pulmonary assessment	Boosting	131 subjects	82.00
Reljin et al., 2020 [33]	Lung fluid accumulation detection	SVM	52 subjects	92.00

Table A.15: Sleep health related studies.

Author, Year	Objective	Approach	Dataset	ACC (%)
Uçar et al., 2016 [122]	Sleep staging	SVM	10 patients	80.00
Malik et al, 2018 [123]	Sleep-wake classification	CNN	56 participants	91.90
Nakayama et al., 2019 [124]	Apnea detection	CART	61 participants	85.00
Wang et al., 2019 [125]	Rapid eye movement detection	RF	45 participants	84.00
Bozkurt et al., 2019 [126]	Apnea prediction	SC	10 participants	93.81
Wang et al., 2019 [127]	Predict sleep apnea	CNN	10 participants	94.40
Haghayegh et al., 2020 [128]	Sleep staging	CNN	1839 participants	84.50
Fonseca et al., 2020 [129]	Sleep staging	RNN	291 participants	75.90
Chen et al., 2020 [130]	Sleep-wake detection	RNN	11 subjects	96.40
Faust et al., 2020 [15]	Apnea detection	RNN	35 recordings	99.80
Martín-Montero et al., 2020 [131]	Apnea detection	ANN	1738 participants	91.70
Singh et al., 2020 [132]	Apnea detection	SVM	35 recordings	81.06
Shen et al., 2021 [133]	Apnea detection	CNN	16988 participants	89.40
Ye et al., 2021 [134]	Apnea detection	CNN	35 recordings	99.22
Goldammer et al., 2021 [135]	Sleep staging	Hybrid	5036 subjects	88.89