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Machine learning–based analysis of non-invasive measurements for predicting intracardiac pressures

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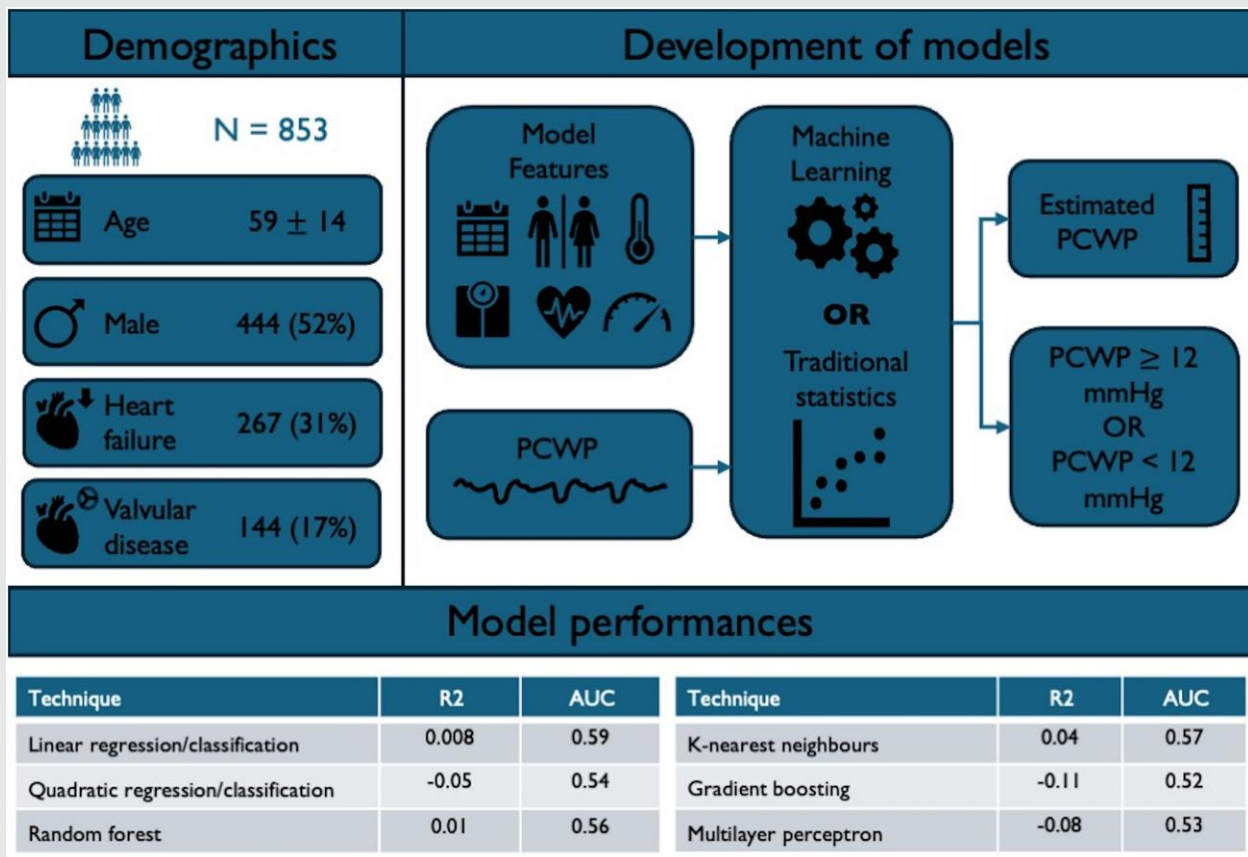|	
Aims	Early detection of congestion has demonstrated to improve outcomes in heart failure (HF) patients. However, there is limited access to invasively haemodynamic parameters to guide treatment. This study aims to develop a model to estimate the invasively measured pulmonary capillary wedge pressure (PCWP) using non-invasive measurements with both traditional statistics and machine learning (ML) techniques.
Methods and results	The study involved patients undergoing right-sided heart catheterization at Erasmus MC, Rotterdam, from 2017 to 2022. Invasively measured PCWP served as outcomes. Model features included non-invasive measurements of arterial blood pressure, saturation, heart rate (variability), weight, and temperature. Various traditional and ML techniques were used, and performance was assessed using R^2 and area under the curve (AUC) for regression and classification models, respectively. A total of 853 procedures were included, of which 31% had HF as primary diagnosis and 49% had a PCWP of 12 mmHg or higher. The mean age of the cohort was 59 ± 14 years, and 52% were male. The heart rate variability had the highest correlation with the PCWP with a correlation of 0.16. All the regression models resulted in low R^2 values of up to 0.04, and the classification models resulted in AUC values of up to 0.59.
Conclusion	In this study, non-invasive methods, both traditional and ML-based, showed limited correlation to PCWP. This highlights the weak correlation between traditional HF monitoring and haemodynamic parameters, also emphasizing the limitations of single non-invasive measurements. Future research should explore trend analysis and additional features to improve non-invasive haemodynamic monitoring, as there is a clear demand for further advancements in this field.

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Graphical Abstract

Demographics

N = 853

Age	59 ± 14	
Male	444 (52%)	
Heart failure	267 (31%)	
Valvular disease	144 (17%)	

Development of models

Model Features → Machine Learning — Gears OR Traditional statistics → Estimated PCWP / PCWP ≥ 12 mmHg OR PCWP < 12 mmHg

PCWP

Model performances

Technique	R2	AUC
Linear regression/classification	0.008	0.59
Quadratic regression/classification	-0.05	0.54
Random forest	0.01	0.56

Technique	R2	AUC
K-nearest neighbours	0.04	0.57
Gradient boosting	-0.11	0.52
Multilayer perceptron	-0.08	0.53

Introduction

Heart failure (HF) is a global pandemic affecting ~63 million patients worldwide, and its prevalence is projected to rise by 43% due to the ageing of the population.[1–3] Despite major advancements in HF management over the last decades, it remains a disease associated with a poor prognosis.[4] Additionally, HF places a significant burden on the healthcare system due to frequent outpatient follow-up and recurrent hospitalization for worsening HF (WHF).[5] The primary reason for HF hospitalization is congestion, and solutions targeting early recognition could prevent subsequent readmissions, thereby significantly reducing the burden of HF care.[6] The gold standard measure of congestion is left arterial pressure; the pulmonary capillary wedge pressure (PCWP), as measured during right-sided heart catheterization (RHC), serves as the accepted surrogate for this measurement.[6,7] The development of implantable sensors measuring the diastolic pulmonary artery (PA) pressure as a surrogate measurement of the left arterial pressure has made it possible to use this information for the remote monitoring of HF patients and has shown to reduce HF hospitalizations and improve quality of life.[8–11] Although the use of such implantable sensors is an effective solution, these systems are invasive and expensive and therefore not available for every HF patient. Currently, non-invasive remote monitoring of HF patients relies on measurements of vital signs,

such as heart rate, blood pressure, and saturation, along with the assessment of signs and symptoms; however, no specific non-invasive methods exist for monitoring PA pressure. While clinical monitoring is effective at identifying existing congestive symptoms, it is unreliable to predict subclinical congestion and guide therapeutic decisions to prevent WHF. Hence, a significant need exists for non-invasive alternatives capable of measuring haemodynamic parameters, allowing for proactive remote monitoring similar to what invasive methods offer. Therefore, the primary aim of this study is to create different models that use non-invasively collected clinical parameters such as vital signs to estimate the PCWP using both traditional statistics and machine learning (ML) techniques.

Methods

Study design and population

In this retrospective study cohort, patients older than 18 years who underwent RHC between 23 June 2017 and 19 August 2022, at the Erasmus MC, were included. Patients were excluded if they had a left ventricular assist device implanted. Patient data were extracted from the electronic health record system and stored in a secured database open for reuse. The extracted data consisted of patient characteristics and clinical characteristics.

The study was approved by the ethics committee (MEC-2022-0822). The complete study method is summarized and visualized in Supplementary material online, *Figure S1*.

Patient characteristics and clinical parameters

In terms of patient characteristics, we collected demographic information, including age and gender, and medical history, which encompassed the presence of HF and/or valvular disease. Concerning the clinical parameters, we gathered data on mean arterial blood pressure (MAP), saturation, heart rate, weight, height, and body temperature. Additionally, heart rate variability (HRV) was derived from electrocardiogram (ECG) signals obtained during catheterization using a MATLAB algorithm. Detailed information about the calculation of HRV is available in the Supplementary material. All clinical data were included only when measured within 72 h before or after the RHC.

Outcome measure

The PCWP was measured during RHC for the PCWP prediction models. Pulmonary capillary wedge pressure served as both a continuous outcome and a categorical outcome (low PCWP: <12 mmHg and high PCWP: ≥12 mmHg). This cut-off value was selected as normal wedge pressures ranging from 4 to 12 mmHg.[12] Right-sided heart catheterization was conducted via the jugular or femoral vein using a Merit Medical Criticath® thermodilution catheter. Since PCWP can be measured multiple times during a catheterization, only the last recorded value was used.

Data pre-processing

After data extraction, patients without the outcome measure (PCWP) were removed, and features with over 20% missing values or patients with over 50% missing features were excluded. Subsequently, the data were randomly divided into a 20% validation data set and an 80% training data set. Then, all features were scaled based on the training data, and any remaining missing values were replaced using multiple imputation. The Pearson correlations between the features were assessed, and for feature sets with a correlation higher than 0.5, only the feature with the highest Pearson correlation with the PCWP was retained, while the other features were discarded.

Model development and evaluation

To approximate the PCWP based on the features, both regression and classification models were used. These models were all trained using the same train-validation split as in the pre-processing phase. For the outcome measure of the regression and classification models, the continuous and categorical PCWP values were utilized, respectively. Traditional statistical methods (i.e. linear regression, quadratic regression, and linear and quadratic discriminant analysis) were directly fitted on the training data set. For the traditional regression models, a linear function (see Supplementary material online, *Figure S5A*) and a quadratic function (see Supplementary material online, *Figure S5B*) were fitted on the training data to estimate the continuous PCWP values. To create the quadratic curves, the data set was expanded by including the square of the features. Similarly for the classification model, both linear and quadratic curves were fitted to separate the training data into low and high PCWP categories. The scikit-learn methods used for this purpose included linear regression for the regression models and linear discriminant analysis or quadratic discriminant analysis for the classification models. In contrast, for the ML algorithms, the training data were further divided into five folds to optimize the model hyperparameters. Multiple ML methods [i.e. *k*-nearest neighbours, random forest, multi-layer perceptron (deep learning), and gradient boosting] were used to construct both regression and classification models. A detailed description of the models included in this study is available in Supplementary material online, *Supplement S1.4*. In this study, 10 randomly selected value combinations of hyperparameters were tested for each ML model. The predefined options for the hyperparameter values can be found in Supplementary material online, *Table S1*. The combination of hyperparameter values that exhibited the best performance after five-fold cross-validation was selected and then fitted on the complete training data set. After the regression and classification models were constructed based on the training data, both the resulting traditional statistical model and the ML model were applied to the validation data to assess their performance. Model performance for the regression and classification models was evaluated using the coefficient of determination (R^2) and the area under the curve (AUC) of the receiver operator characteristics (ROCs) curve, respectively. Data pre-processing and statistical analysis were performed using Python, utilizing the following packages: Python library scikit-learn, and XGBoost.

Secondary analyses

To assess whether the model performances vary within more specific and homogeneous populations, the primary regression analysis was repeated by including solely HF patients and thereafter, by only including patients without valvular disease.

Results

From 1007 RHCs conducted, 853 RHCs from 791 unique patients satisfied the inclusion criteria and had sufficient available data (see Supplementary material online, *Figure S2*). The mean age of the patients was 58.9 years (SD ±13.7), with 47.9% being female. Among these patients, 31.3% had HF and 16.9% had some form of moderate-to-severe valve disease. The mean PCWP value was 13.1 mmHg (SD ±8.6), and 48.7% of the values were 12 mmHg or higher. There were no significant differences between the training and the validation data sets (*Table 1*).

Table 2 shows the Pearson correlation coefficients between the clinical parameters and the PCWP in the entire population and in subpopulations. Scatterplots visualizing the PCWP distributions per clinical parameter can be found in Supplementary material online, *Figure S3*. Overall, all individual clinical parameters displayed weak correlations with PCWP, with HRV having the highest correlation of 0.16 in the complete population.

Primary and secondary outcomes

Table 3 presents the performances of the various regression and classification models. The clinical parameters included in these models were age, gender, weight, heart rate, saturation, body temperature, MAP, and HRV. Overall, the regression models exhibited weak performances (R^2 values: −0.12 to 0.04). In the best-performing model, with an R^2 value of 0.04, the *k*-nearest neighbour method was used. The classification algorithms for low (<12 mmHg) and high PCWP (≥12 mmHg) also showed poor performances with AUC values between 0.52 and 0.59 (*Table 3*). The linear classification model yielded the best performance (AUC: 0.59). All ROC curves are visualized in *Figure 1*.

In *Table 4*, the results of the subgroup analysis are shown. When analysing only patients with HF, the R^2 values for every regression model were negative (R^2 values: −0.44 to −0.03), meaning that the models' performance was worse than when estimating the PCWP using the mean of the data. Similarly, excluding patient valve disease resulted in worse performance compared with the primary analysis (R^2 values: −0.78 to 0.04).

Discussion

In this retrospective cohort of 791 patients who underwent RHC, we demonstrated that the currently used clinical parameters showed limited correlation with invasively measured PCWP values. Moreover, we were unable to accurately approximate the invasively measured PCWP using clinical patient characteristics and non-invasively measured vital signs, using both traditional statistical and ML techniques. Overall, our study suggests that the current selection of non-invasive vital parameters measured at a single time point is not correlated to and reflective of the patient's volume status, for which PCWP is the reference value.

Table 1 Population characteristics of the total data set, training data set, and validation data set

	Total data set (N = 853)	Training data set (N = 682)	Validation data set (N = 171)
Demographics and medical history			
Age (years), mean ± SD	58.9 ± 13.7	59.1 ± 13.4	58.2 ± 15.2
Male, n (%)	444 (52.1)	361 (52.9)	83 (48.5)
Heart failure, n (%)	267 (31.3)	213 (31.2)	54 (31.6)
Heart valve disease, n (%)	144 (16.9)	115 (16.9)	29 (17.0)
Haemodynamic parameters			
PCWP (mmHg)	13.1 ± 8.6	13.0 ± 8.4	13.2 ± 9.1
PCWP ≥ 12 mmHg, n (%)	415 (48.7)	338 (49.6)	77 (45.0)
Vital parameter, mean ± SD			
Weight (kg)	78.3 ± 17.5	78.4 ± 17.3	78.1 ± 18.0
Heart rate (b.p.m.)	77.5 ± 14.4	77.4 ± 14.1	78.1 ± 15.7
HRV (ms)	80.7 ± 65.4	80.9 ± 66.8	80.1 ± 59.3
MAP (mmHg)	88.3 ± 13.9	88.1 ± 13.5	89.3 ± 15.4
Saturation (%)	95.4 ± 2.9	95.4 ± 2.9	95.3 ± 2.8
Temperature (°C)	36.5 ± 0.5	36.5 ± 0.4	36.6 ± 0.5

SD, standard deviation; PCWP, pulmonary capillary wedge pressure; HRV, heart rate variability; MAP, mean arterial pressure.

Table 2 Pearson correlation coefficients between the features and the pulmonary capillary wedge pressure for different subpopulations sorted by absolute correlation in the total population

	All	HF	No valve disease	HF without valve disease
	(n = 853)	(n = 267)	(n = 609)	(n = 178)
Age	0.04	0.01	0.03	0.07
Gender	0.09	0.11	0.11	0.10
Weight	0.09	0.07	0.10	0.04
Heart rate	−0.04	−0.02	−0.03	−0.01
HRV	0.16	0.11	0.16	0.21
MAP	−0.10	−0.09	−0.09	−0.08
Saturation	0.00	−0.07	−0.02	−0.07
Temperature	0.01	0.05	0.01	0.07

HRV, heart rate variability; MAP, mean arterial pressure.

Table 3 Performance results of the primary analysis

Technique	Regression R^2	Classification AUC
Linear regression/classification	0.008	0.59
Quadratic regression/classification	−0.05	0.54
Random forest	0.01	0.56
k-nearest neighbours	0.04	0.57
Gradient boosting	−0.11	0.52
Multi-layer perceptron	−0.08	0.53

R^2, coefficient of determination, AUC, area under the curve.
For every technique, a regression model and a classification model were built and validated, resulting in an R^2 value for every regression model and an AUC value for every classification model.

Our findings present a contrast to the non-invasive telemonitoring systems commonly utilized for HF patients in current clinical practice, which heavily rely on vital sign measurements. A recent meta-analysis showed that these systems are significantly reducing clinical endpoints such as all-cause mortality and HF hospitalizations.[13] The results of our study when compared with the effectiveness of non-invasive telemonitoring systems may be explained by several reasons. To develop a valuable predictive model, measurements that provide useful information about the patient's current clinical status or predict future events are essential. As previously shown, most clinical parameters do not accurately reflect the volume status of the patient. For example, body weight, which is simple to measure and often used to monitor HF patients, has several shortcomings. Weight can be influenced by the patient's clinical condition, fluctuations in food and fluid intake, and the effectiveness of diuretic therapy (which may be inappropriately dosed). Many patients either do not experience weight gain or experience only minor increases before a WHF event. Additionally, research has indicated that weight changes have a notably low sensitivity in detecting HF deterioration.[14] This poor correlation between other symptoms or physical signs has recently also been shown by Polcz et al.[15] While it may be accurate that there appears to be no correlation between vital signs and invasively measured intracardiac pressures, our hypothesis was that this lack of correlation could be attributed to limitations in uncovering this relationship through conventional statistical methods. Nevertheless, even after applying ML, which offers new opportunities for exploring the correlation between PCWP and vital signs, we were unable to identify a correlation or estimate the PCWP. Another hypothesis could be that non-invasive telemonitoring systems rely on longitudinal follow-up of patients. The models in the current study aimed to estimate a single PCWP with clinical parameters from a single time point. Accordingly, the absolute magnitude of the parameter itself might be of secondary importance, as it is the change in both PCWP and clinical parameters that carries greater significance. From a clinical perspective, these variations are more significant for decision-making than the absolute values
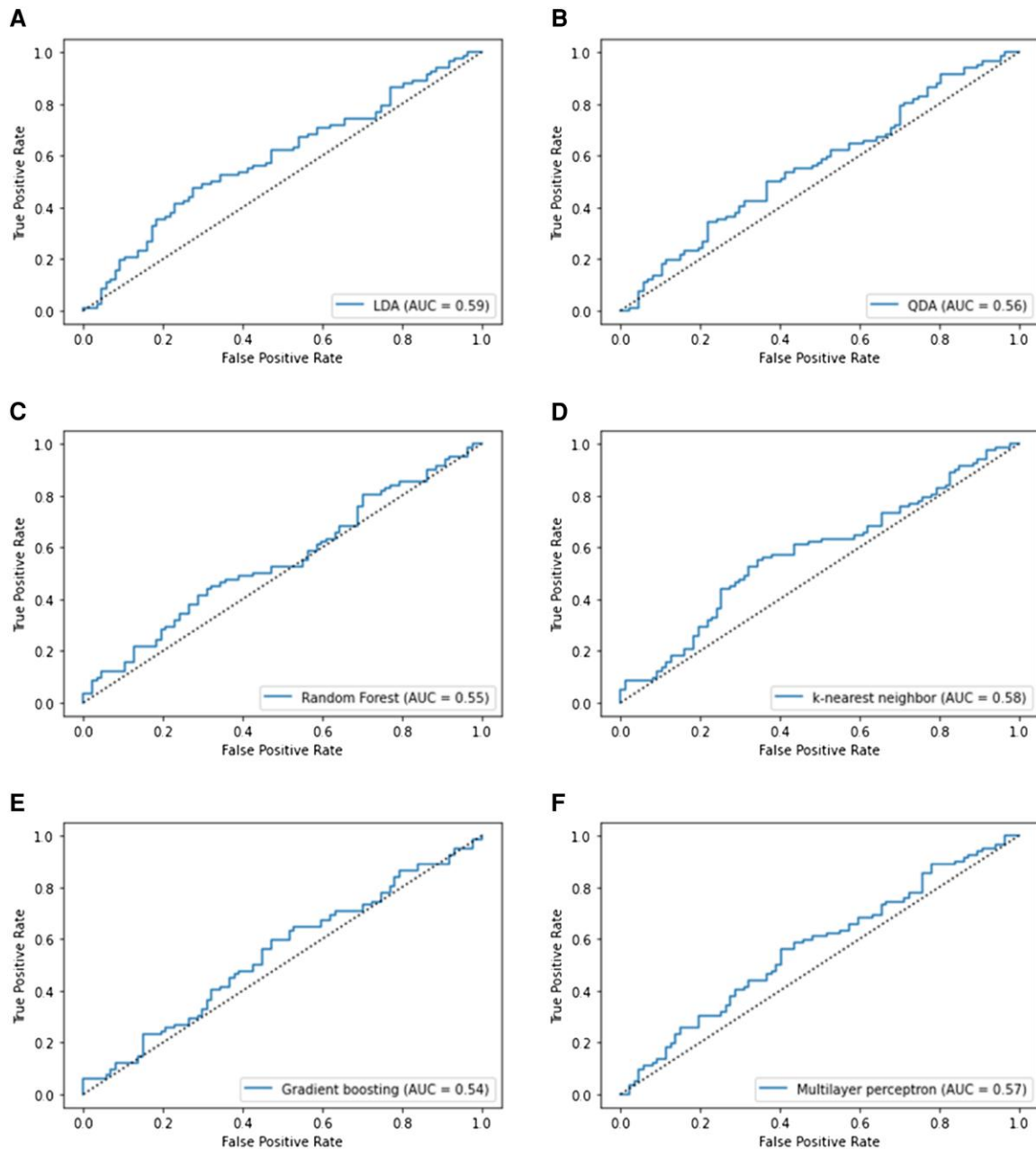
Figure 1 Receiver operator characteristics plots of the classification models. (*A*) A linear discriminant analysis classifier; (*B*) a quadratic discriminant analysis classifier; (*C*) a random forest; (*D*) *k*-nearest neighbour; (*E*) gradient boosting; (*F*) a multi-layer perceptron.

of vital parameters. Lastly, the observation that a single vital parameter may not directly correlate with patient filling pressures aligns with expectations, as non-invasive telemonitoring systems often integrate a variety of data sources, including clinical information on HF symptoms, rather than relying solely on vital signs. This comprehensive approach underscores the limited utility of individual vital signs in accurately assessing fluid status, highlighting the critical role of clinical information in achieving a holistic understanding of the patient's condition and volume status. Supporting this reasoning, structured telephone support that involves obtaining detailed information about signs and symptoms appears to outperform other categories of non-invasive remote monitoring.[13] As such, the current data offer both an appreciation of the

abilities and limitations of the importance of the history and physical exam and longitudinal follow-up in the care of HF patients.

Future perspectives

This study shows that a single measurement for vital signs does not provide sufficient information about the patient's volume status reflected by the PCWP. Nonetheless, a significant demand for non-invasive alternatives to measure intracardiac pressures remains. However, the prerequisite for a suitable tool to aid the clinical assessment of HF is that it can provide accurate measurements that are, in absolute terms, similar to those of the invasive haemodynamic gold

Table 4 Performance results of the secondary analyses

Technique	HF R^2 (n = 267)	No valve disease R^2 (n = 609)
Linear regression	−0.11	−0.03
Second-degree regression	−0.32	−0.78
Random forest	−0.06	−0.08
k-nearest neighbours	−0.03	0.04
Gradient boosting	−0.45	−0.09
Multi-layer perceptron	−0.28	−0.48

HF, heart failure; R^2, coefficient of determination.
For every regression technique, a model was built and validated per data or feature subgroup. The four subgroups were as follows: all HF patients with non-invasive features, all patients without valve disease with non-invasive features, all patients with only additional features, and all patients with all the features (non-invasive and additional).

standard. Future prospective studies should evaluate the clinical value of trends in clinical parameters, which can involve single measurements like heart rate, respiratory rate, and weight. Additionally, the accessibility and convenience of wearable devices, based on photoplethysmography (PPG) or ECG signals, can enable more frequent measurements of vital signs for remote monitoring of HF patients. Measurements can be performed by adequately validated consumer-grade wearables such as the Apple Watch and Fitbit, which have the capability to measure heart rate or HRV through PPG sensors.[16,17] Specifically, HRV, which is related to autonomous dysregulations, is part of the cascade leading to a WHF event and may consequently be associated with elevated PCWP. Unfortunately, in our study, the HRV was poorly related to PCWP, possibly due to the brief duration of HRV measurement (5 min). Heart rate variability can potentially provide additional value when measured continuously over a prolonged period using a wearable device. Alternatively, dedicated devices such as the VitalPatch described by Stehlik et al.[18] are also suitable. Rather than striving to estimate the PCWP with vital signs, this device provides an index value based on an incorporated ML algorithm capable of predicting HF readmissions with reasonable accuracy.

Furthermore, there is a potential to utilize raw pre-processed ECG or PPG data to enhance the ML pipeline by sophisticated feature generation techniques to uncover new data patterns. In a study by Raghu et al.,[19] a deep learning model utilizing ECG features identified patients with a PCWP exceeding 18 mmHg, achieving an AUC of 0.82. These encouraging findings imply the potential benefits of enhancing the non-invasive feature set by incorporating additional ECG features.

More importantly, utilization of these devices opens up the possibility of exploring the relationship between raw biosignals obtained from multiple sensors and invasively measured intracardiac pressures, moving away from relying on vital signs as a proxy. Several non-invasive haemodynamic monitoring tools have already advanced beyond the conceptual stage as a result of this progression. Two notable examples include the Cardiosense CardioTag, a wearable ECG and seismocardiogram (SCG) sensing patch, and an ML algorithm for estimating continuous blood pressure, change in cardiac output, and PCWP. A proof-of-concept study confirmed accuracy in PCWP estimation for 20 patients.[20] The Acorai device, another device utilizing the SAVE sensor system incorporating ECG, SCG, PPG, and phonocardiography sensors, showed moderate correlation with intracardiac pressures.[21] Ongoing refinement of these non-invasive devices expands the possibilities in haemodynamic monitoring, potentially optimizing therapies and improving outcomes.

Limitations

Our study has several limitations. First of all, the PCWP measurements were not obtained simultaneously with all other features used in our models. In our study, we utilized the closest measured value within a window of 72 h before and after the RHC, rather than during the catheterization itself. Therefore, some feature values included in our models may differ from the actual feature values at the time of catheterization. However, this approach represents the closest possible estimation of the feature values. Second, our models are based on features measured on a single moment in time. Longitudinal data from both PCWP and clinical parameters are needed to investigate whether clinical parameters are of value in estimating the change in PCWP over time. Third, the catheterizations performed in our retrospective data set had a wide variety of indications, resulting in diverse patient characteristics. This may have resulted in a limited ability to accurately approximate the PCWP. However, in our subgroup analyses, the accuracy of the models did not improve. In addition, by making this subgroup analysis, the models are tailored to a specific patient category, e.g. HF patients without valvular disease. As a result, the models may not apply to the 'real-world' HF patients, in which valvular disease is a frequent co-morbidity. Lastly, due to missing outcome data and data on clinical parameters, a relatively small proportion of the patients (n = 154) could not be included in the analysis, potentially biasing our current findings.

Conclusions

In this large retrospective study, we were unable to estimate invasively measured intracardiac pressures from clinical parameters using both traditional statistics and ML techniques. Our results underline the shortcomings of sporadic measurements of non-invasive measurements and emphasize the need for future studies incorporating trend analyses and generation of features out of raw data signals. Nevertheless, there is a significant demand for innovative advancements in the field of non-invasive (haemodynamic) remote monitoring.

Supplementary material

Supplementary material is available at European Heart Journal – Digital Health.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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