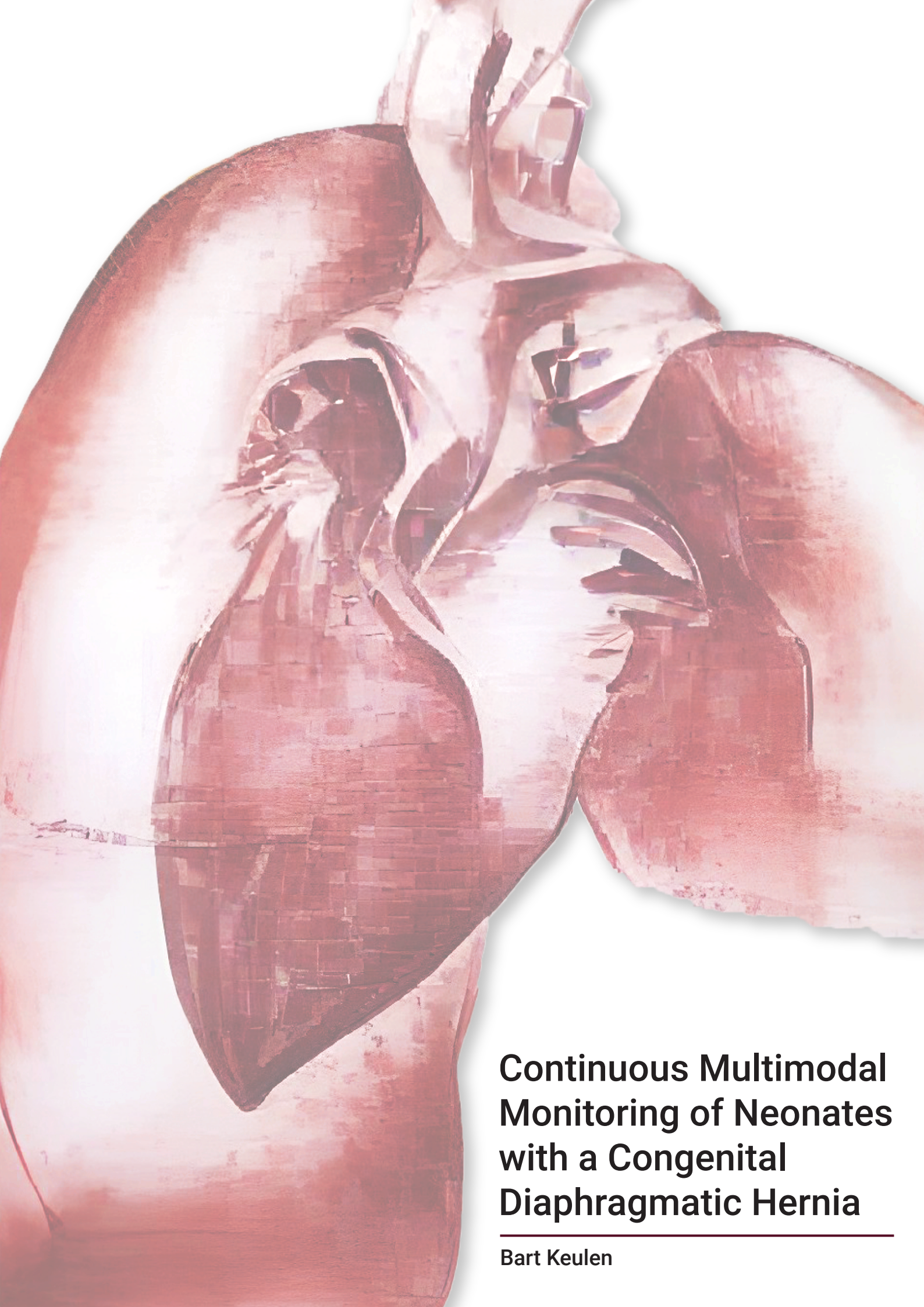

Continuous Multimodal Monitoring of Neonates with a Congenital Diaphragmatic Hernia

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Continuous Multimodal Monitoring of Neonates with a Congenital Diaphragmatic Hernia

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Preface and Acknowledgements

It feels somewhat weird to put the finishing touches to this thesis because it means that in about two weeks, my time as a student will have come to an end. During this time, I have gained a significant amount of medical and technical knowledge and acquired many useful skills. Perhaps even more importantly, I have also undergone major personal developments. During the internships in the last few years, I learnt to apply but also appreciate this set of knowledge and skills. With each internship, I felt more confident about my own qualities, leading to an increasing sense of ownership over my projects.

In early 2022, I found out about the existence of the Children's Thoraxcenter of the Sophia Children's Hospital. The idea of a combination of cardiopulmonary diseases and paediatrics was followed by excitement, which showed me that I should explore that idea further. Within a few weeks, that idea evolved into a thesis project, and my excitement grew even further. Now, almost a year later, I have explored the challenges in paediatric acute care, the complexities of statistical analyses, and the difficulties of measuring and managing the enormous amount of PICU data. I proudly look back on a fruitful period, not only because of my personal development but also because I believe that this project could lead to further improvement in the care of patients with CDH.

During the course of this graduate internship and the writing of this thesis, many people have helped and guided me through this process. First of all, I would like to express my deepest appreciation to my supervisors, Suzan Cochius, Frank Gijsen, Eris van Twist, and Marco Schnater. Suzan, thank you for your constructive feedback, openness to suggestions, and advice on the medical part of this project. During our discussions I have always felt more an equal colleague rather than a student, something which I have truly appreciated. Frank, thank you for your technical look on the project and the down-to-earth feedback. You often helped me to regain focus on what was important at that time. Eris, your close involvement, enthusiasm, and endless helpfulness could not have been missed, for which I am deeply grateful. Marco, this whole endeavour would not have been possible without your willingness to initiate this project. For that, I am thankful.

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Lastly, I would be remiss not to mention my friends, family, and Annabel who have provided advice and a listening ear when needed. You have often helped me get my feet back on the ground and were just there whenever I needed someone to vent to. However small, such gestures do make a difference and I thank you for that.

Bart Keulen

Abstract

Introduction

Congenital diaphragmatic hernia (CDH) is a rare developmental defect of the diaphragm characterised by herniation of abdominal organs into the thoracic cavity during prenatal development. This herniation is usually accompanied by pulmonary hypertension (PH) and cardiac dysfunction (CD). Although several parameters are known to predict the clinical outcomes in CDH, most of these parameters do not monitor the degree of PH and CD and cannot be continuously measured. This retrospective observational trial aimed to monitor the degree of PH and CD in CDH using the oxygen saturation index (OSI), peripheral oxygen saturation (SpO_2), heart rate (HR), heart rate variability (HRV), arterial blood pressure (ABP) and derivatives of these parameters.

Methods

The study population consisted of neonates admitted to the paediatric intensive care unit between 2019 and 2022 for treatment of CDH. The degree of PH and CD was determined for each cardiac ultrasound (CUS) performed. A 15-minute window of vital parameters, mechanical ventilator, and electrocardiogram data before each CUS was extracted to calculate the predictors. After preprocessing the data and meeting the statistical assumptions, both univariable and multivariable logistic mixed effects models were fitted and validated.

Results

In total, 136 CUS of 57 patients were included in the study. Of the univariable linear mixed-effects models, the median values of HR, pulse pressure (PP), preductal SpO_2, $dSpO_2$, OSI and the interquartile range (IQR) of HR were statistically significant predictors of PH. For the prediction of CD, this was the case for the power of HRV in the very low frequency band (HRV-VLF) and for the median values of HR, mean arterial pressure (MAP) and OSI. The multivariable model for the prediction of PH contained the median values of of $dSpO_2$, HR, PP and OSI and the standard deviation of the normal-to-normal beat intervals (SDNN). The multivariable model for the prediction of CD included the median of $dSpO_2$, HRV-VLF, SDNN and the IQR of SAP as predictors.

Conclusions

The most promising predictors are the median values of preductal SpO_2, $dSpO_2$ and OSI for the prediction of PH. For the prediction of CD, HRV-VLF and the median values of HR, OSI and $dSpO_2$ were the most promising predictors. Despite limited predictive performance of the regression models, this study contributes to the improvement of monitoring of patients with CDH, which can lead to more timely interventions and eventually improved outcomes within this patient population.

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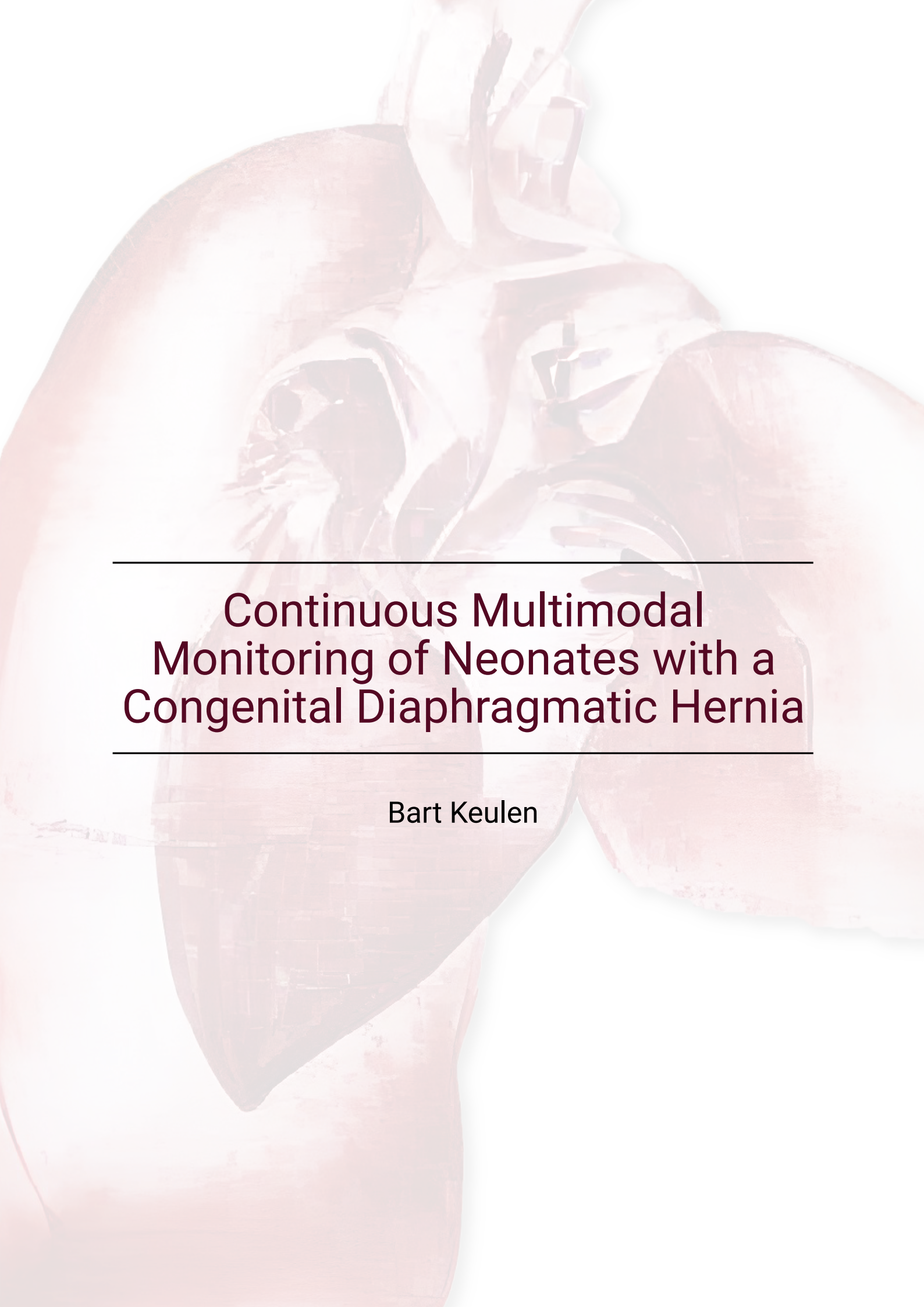
List of Abbreviations

ABP	arterial blood pressure
AIC	Akaike information criterion
CD	cardiac dysfunction
CDH	congenital diaphragmatic hernia
CUS	cardiac ultrasound
CVP	central venous pressure
DAP	diastolic arterial blood pressure
$dSpO_2$	difference between preductal and postductal SpO2
ECG	electrocardiography
ECMO	extracorporeal membrane oxygenation
EHR	electronic health record
FiO_2	fraction of inspired oxygen
HR	heart rate
HRV	heart rate variability
HRV-HF	spectral power of HRV in the high frequency band (0.15-0.40 Hz)
HRV-HFn	HRV-HF normalised to the total spectral power
HRV-LF	spectral power of HRV in the low frequency band (0.04-0.15 Hz)
HRV-LF/HF	ratio of LF to HF
HRV-LFn	HRV-LF normalised to the total spectral power
HRV-VLF	spectral power of HRV in the very low frequency band (0.0033-0.04 Hz)
IQR	interquartile range
LMEM	logistic mixed effects model
LOO-CV	leave-one-out crossvalidation
MAP	mean arterial blood pressure
NPV	negative predictive value
O/E LHR	observed-to-expected lung-to-head ratio

OI	oxygenation index
OSI	oxygen saturation index
P_{aw}	mean airway pressure
PaO_2	partial pressure of oxygen in arterial blood
PAP	pulmonary arterial pressure
PH	pulmonary hypertension
PICU	paediatric intensive care unit
PLS	heart rate measured using oximetry
PP	pulse pressure; difference between systolic and diastolic arterial pressure
PPV	positive predictive value
PVC	premature ventricular complex
QQ-plots	quantile-quantile plots
SAP	systolic arterial blood pressure
SDNN	standard deviation of beat-to-beat intervals of normal R-peaks
SpO_2	peripheral oxygen saturation



Continuous Multimodal Monitoring of Neonates with a Congenital Diaphragmatic Hernia

Bart Keulen

1 | Introduction

1.1 Congenital diaphragmatic hernia

Congenital diaphragmatic hernia (CDH) is a rare developmental defect of the diaphragm characterised by herniation of the abdominal organs into the thoracic cavity during prenatal development. The prevalence of CDH is estimated to vary between 1.7 and 5.7 per 10.000 births, depending on the study population and geographical region. [1–3] Most patients (85%) present with a left-sided defect, and in 50%-70% of cases, CDH occurs as an isolated defect. [4] The remaining 30%-50% of cases, nonisolated or complex CDH, are associated with chromosomal disorders, single-gene disorders, or structural anomalies of the cardiovascular, central nervous or musculoskeletal systems. [4, 5]

The herniation of abdominal organs is accompanied by pulmonary hypoplasia and abnormal pulmonary vasculature, leading to pulmonary hypertension (PH). [5–7] Patients typically present with hypoxemic respiratory failure and shock. Hypoxemia occurs mainly due to intrapulmonary shunting and extrapulmonary right-to-left shunting across the foramen ovale and ductus arteriosus. [8] In patients with severe PH, the right-to-left shunting across the ductus arteriosus results in significant differences between preductal and postductal arterial blood gas measurements. [9] In most patients, PH resolves within the first weeks of life, although persistent PH predicts morbidity and mortality. [10, 11]

In addition to pulmonary abnormalities, cardiac dysfunction (CD) of either or both ventricles is also frequently seen in CDH and is associated with mortality. [7, 12–17] Primary dysfunction of the left ventricle in CDH is often a combination of left ventricular hypoplasia with an increase in left ventricular afterload after birth and a reduced preload of the left ventricle due to a lower pulmonary blood flow. [7] Right ventricular hypertrophy is also a common finding in CDH and is caused by an elevated afterload of the right ventricle due to PH. Right ventricular hypertrophy and displacement of the interventricular septum may cause a secondary dysfunction of the left ventricle due to the interdependence of the two ventricles. [7]

With PH and CD being two of the key pathophysiologies of CDH, the treatment is primarily focused on treatment of PH and management of ventilation and haemodynamics. [2, 5, 18] The survival of CDH is reported to be around 60%-90% and is generally lower in low- and middle-income countries and in patients who require extracorporeal membrane oxygenation (ECMO). [2, 3, 6, 19]

1.2 Predictors of clinical outcome

Different parameters have been shown to be predictive of outcomes in CDH. In the prenatal period, a low observed-to-expected lung-to-head ratio (O/E LHR), low estimated lung volumes measured during MRI, and herniation of the liver into the thoracic cavity are associated with poorer outcomes. [2, 5, 6, 20–23] Mortality and the need for ECMO are associated with postnatal patient characteristics such as gestational age and birth weight, and with parameters such as right ventricular systolic pressure, preductal SpO_2 and the partial pressure of oxygen in postductal arterial blood (PaO_2). [11, 20, 23–26] A model developed by the Congenital Diaphramatic Hernia Study Group uses, among others, birth weight and the Apgar score at 5 minutes of life to calculate the probability of survival. [27] Another parameter predictive of outcomes in CDH is the oxygenation index (OI), calculated as

$$OI = \frac{FiO_2 \cdot \bar{P}_{aw}}{PaO_2}, \tag{1}$$

with $\bar{P}_{aw}$ the mean airway pressure in cmH_2O, FiO_2 the fraction of inspired oxygen as a percentage and PaO_2 in kPa. [20] It has been shown that OI in the first hours and days of life is predictive of both ECMO and mortality in patients with CDH. [20, 25, 28, 29]

The downside of most of the aforementioned predictors of outcomes in CDH is that they cannot be continuously monitored and often require invasive measurement techniques. Next, most of these parameters are prognostic of

outcomes and cannot be used for monitoring. Although monitoring of the degree of PH and CD as two of the key pathophysiologies in CDH is possible, it is usually done using cardiac ultrasound (CUS), which is stressful for these critically ill patients and lacks the possibility of continuous monitoring. [10, 12] Continuous and non-invasive monitoring of relevant parameters indicative of the degree of PH and CD would provide significant added value in clinical practice. Early detection of changes in the patient's condition will lead to more timely interventions and consequently to improvements in overall outcomes. This led to the question of which parameters can be used for continuous monitoring of PH and CD in CDH.

1.3 Study objectives

This retrospective observational trial aimed to determine which continuously measured parameters can be used to monitor the degree of PH and CD in neonates with CDH. This main goal has been divided into five objectives:

1. providing a background on the parameters that will be used in this study, based on the literature and practical considerations (Section 2);
2. processing and calculating potential predictors of PH and CD using continuously measured data from an existing population of neonates with CDH (Section 3.2);
3. classifying the degree of both PH and CD within those same patients according to the CUS performed during their PICU stay (Section 3.3 and 5);
4. determining which predictors are most promising for monitoring the degree of PH and CD of patients with CDH in clinical practice (Section 4);
5. interpreting the results found and their potential clinical use in light of the literature (Section 6).

2 | Background

2.1 Preliminary research

Prior to this study, a literature review was conducted aimed at identifying parameters that have the potential to continuously monitor the cardiac and pulmonary function of neonates with CDH. [30] Of the parameters identified, the premature ventricular complex (PVC) rate was not considered useful as PVCs are not common in CDH. The respiratory rate was also not considered a relevant parameter because all CDH patients are mechanically ventilated for the majority of the PICU stay. Furthermore, cardiac index and central venous pressure (CVP) are not measured in our PICU. The remaining identified parameters were oxygen saturation index (OSI), peripheral oxygen saturation (SpO_2), heart rate (HR), heart rate variability (HRV), and arterial blood pressure (ABP).

Using additional supporting literature, this section will present an overview of the rationale behind the use of each of these parameters and will elaborate on which specific aspects of these parameters will be used for analysis.

2.2 Peripheral oxygen saturation

In a retrospective trial on CDH patients from 2000 to 2010, the highest preductal SpO_2 in the first 24 hours of life was associated with mortality, the use of ECMO therapy and the length of hospital stay. [26] Although predictive of outcomes, the preductal SpO_2 alone is probably only an indirect indication of the degree of PH. With a higher degree of PH and therefore a higher pulmonary arterial pressure (PAP), right-to-left shunting can occur. This shunting will be either intrapulmonary and through the foramen ovale (preductal shunting) or ductus arteriosus (postductal shunt), leading to a decrease in preductal and postductal SpO_2, respectively. [8] Additionally, a lower preductal SpO_2 can also be caused by an pulmonary problem such as lung hypoplasia. This makes it difficult to differentiate between PH and an oxygenation problem in the case of low preductal SpO_2. The difference between the preductal and postductal SpO_2 ($dSpO_2$) might therefore be more indicative of the degree of PH as that difference will be caused by right-to-left shunting through the ductus arteriosus alone. Within this study, the preductal SpO_2 and $dSpO_2$ will be used as well as the postductal SpO_2.

2.3 Oxygen saturation index

OSI is a marker of respiratory failure similar to OI with the difference being that SpO_2 is used instead of PaO_2. [31, 32] PaO_2 is measured in arterial blood samples, which cannot be done continuously. By using the continuously measured SpO_2 instead of PaO_2, continuous monitoring becomes possible. The OSI is thus defined as

$$OSI = \frac{\bar{P}_{aw} \cdot FiO_2}{SpO_2}. \tag{2}$$

OSI correlates strongly with OI and has comparable predictive values for adverse outcomes in CDH. [31] OSI values of CDH patients in the first 24 hours after PICU admission have already been shown to predict PH, the need for ECMO therapy, and mortality. [31, 33]

2.4 Heart rate

HR corrected for age was shown to be a statistically significant predictor of impending cardiac arrest in neonates and infants with cardiac disease. [34] HR was also predictive of survival in adults with cardiogenic shock and acute respiratory distress syndrome. [35, 36] Although no other studies in neonates with pulmonary or cardiac dysfunction have been found on the association between HR and clinical outcomes, the parameter is commonly used as a general indicator of clinical status and therefore used here.

2.5 Heart rate variability

Much research has been conducted on the significance and clinical use of HRV in neonates [37]. HRV refers to alterations in beat-to-beat intervals over time, which results from the balance of inputs from the parasympathic and sympathic nervous system. [37, 38] The most common HRV measures can be divided into time and frequency domain measures.

2.5.1 Frequency domain measures

Based on the different systems that modulate HR at different frequencies, the power spectrum of HRV can be divided into four frequency bands: the ultra-low (ULF; $\leq$ 0.0033 Hz), very low (VLF; 0.0033 - 0.04 Hz), low (LF; 0.04-0.15 Hz), and high (HF; 0.15-0.4 Hz) frequency band. [39] The ULF band is related to low-frequency processes, such as circadian rhythms, but can only be assessed in recordings of at least 24 hours. [39] The VLF band may be regulated by the sympathetic nervous system, physical activity and thermoregulatory and endothelial influences of the heart. [40] Although much is still not known about the VLF rhythm, several studies have shown that it is associated with arrythmic death and inflammation and that it might be intrinsically generated by the heart. [40, 41] The LF band is reflective of sympathic activity and baroreflex activity at rest, and the HF band is reflective of parasympathic activity and corresponds to HR variations caused by respiratory effects. [39, 40]

In a case series of four patients with CDH, the logarithmic transformed power content of HRV in the frequency band of 0.04 to 1.8 Hz was greater than 2 for the two survivors, while the two non-survivors had power values below 2. [42] In addition, a study on neonates and infants with cardiac disease showed that the relative power of HRV in the LF and HF bands (HRV-LF and HRV-HF, respectively) and the $\log_{10}$ ratio of LF to HF (LF/HF) was predictive for impending cardiac arrest. [34] The idea behind HRV-LF/HF is that it is a measure for sympathovagal balance [38, 39], although this idea is controversial as HRV-LF does not represent sympathic activity alone and the values are dependent on the measurement conditions. [40] Furthermore, the fact that there is evidence pointing toward a relationship between intrinsic cardiac function and VLF rhythm makes the total spectral power in the VLF band (HRV-VLF) also an interesting parameter to use here for the prediction of CD. HRV-VLF, HRV-LF and HRV-HF will be used here. HRV-LF and HRV-HF were also normalised (HRV-LFn and HRV-HFn, respectively), to assess their contribution relative to the total power of HRV and to make comparisons between patients and other studies easier. [39]

2.5.2 Time domain measures

The most well-known and most often researched HRV parameter in the time domain is the standard deviation of the normal-to-normal beat interval (SDNN). [37] Normal beats are defined as QRS-complexes following sinus-node depolarisation, excluding technological artefacts and ectopic beats. [38–40] The SDNN reflects all cyclic components related to variability and is the simplest HRV measure in the time domain. [38] The SDNN is also considered the gold standard for estimating cardiac risk. [40]

2.6 Arterial blood pressure

In the preliminary literature review, no studies on the use of ABP in patients with cardiac dysfunction included paediatric patients. [30] Only mean arterial pressure (MAP) and lowest diastolic arterial pressure (DAP) were associated with mortality in three studies in adult patients, but equally often no association was found. [35, 43–45]. In another study, only pulse pressure (PP, defined as the difference between systolic arterial pressure (SAP) and DAP) and SAP were shown to be statistically significant predictors of low left ventricular output in premature born neonates. [46] Because ABP is related to cardiac functioning and is measured in all CDH patients admitted to the PICU, DAP, MAP, SAP, and PP will be calculated and included in the analyses.

3 | Data acquisition and processing

3.1 Patients

The study population consisted of neonates admitted to the PICU of the Erasmus MC Sophia Children's Hospital (Rotterdam, The Netherlands) between 1st of January 2019 and 31th of December 2022 for treatment of CDH. Data on demographics, survival, surgery, and ECMO therapy were collected from the electronic health record (EHR) of each included patient.

3.2 Continuous data

All parameters described in Section 2, with the exception of the HRV measures, are acquired from vital parameter data. For the calculation of OSI, mechanical ventilator data was also needed. HRV measures were calculated using electrocardiogram (ECG) data. In Figure 1, the steps taken in the acquisition and processing of these continuous data and the subsequent calculation of predictors are visualised. These steps will be explained in the next paragraphs. A more detailed description of the artefact detection and removal can be found in Appendix A.

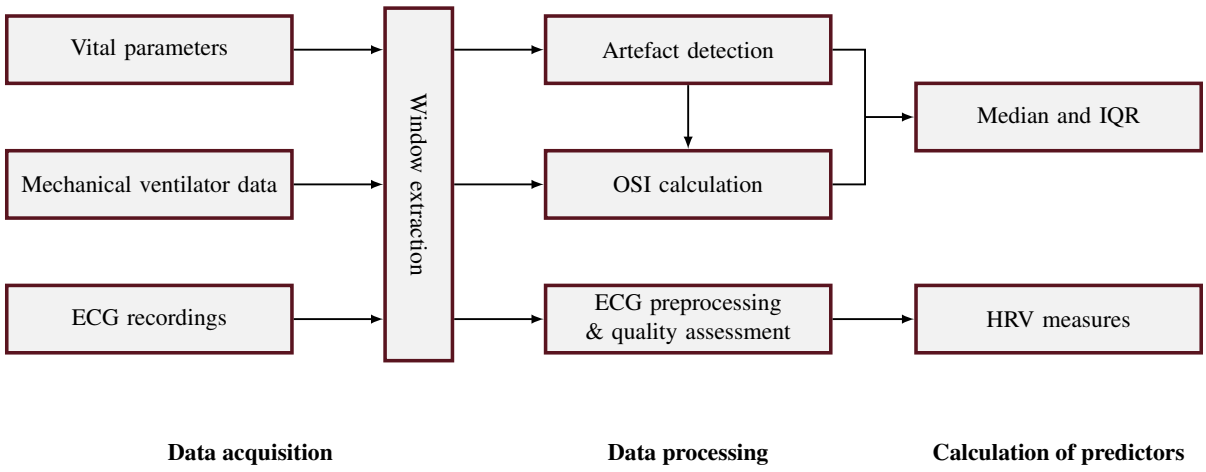


Figure 1: Flowchart of the acquisition and processing of continuous data and the calculation of predictors. ECG = electrocardiogram; OSI = oxygen saturation index; IQR = interquartile range; HRV = heart rate variability

3.2.1 Window extraction

From all data, a 15 minute window prior to each CUS was extracted in order to assess the patient's status at the time of CUS. The use of data measured during or after the CUS was not possible due to noise interference, disconnection of the ECG electrodes from the monitor, and because the CUS can be a stressful experience for patients. A 15-minute buffer was maintained between the window and the CUS to avoid artefacts caused by preparations for the CUS. Consequently, raw data from 30 to 15 minutes before each CUS were extracted from the relevant files.

3.2.2 Vital parameters

All vital parameters measured during the PICU stay were stored on a secure server with a sample frequency of 1 Hz. If measured, the parameters extracted from the secure server were HR measured using ECG electrodes, heart rate measured using pulse oximetry (PLS), preductal and postductal SpO_2, DAP, MAP and SAP. Unfortunately, the preductal and postductal oximetry cuffs were not consistently connected to the same channels on the monitor, resulting in variable and often incorrect data labels in the data files. Because it is not possible for the postductal SpO_2 to be higher than the preductal SpO_2, it was assumed that the parameter with the highest median value was

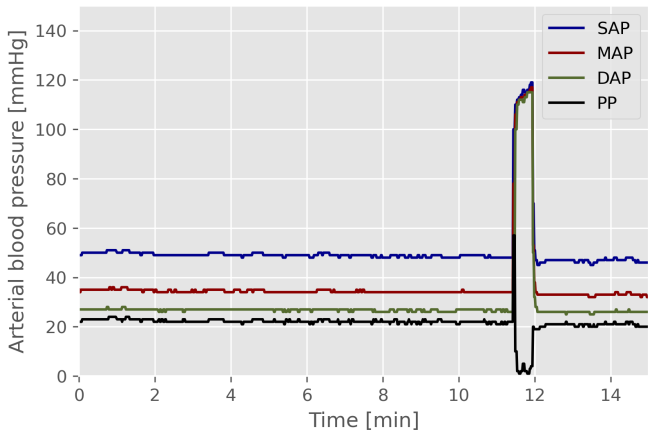


Figure 2: Recording with a rapid increase in arterial blood pressure (ABP). The artefact lasted for around 30 seconds before returning to baseline. This artefact is probably caused by either withdrawal of blood from the arterial line or flushing of the arterial line. SAP, MAP, DAP = systolic, median and diastolic arterial pressure, respectively; PP = pulse pressure.

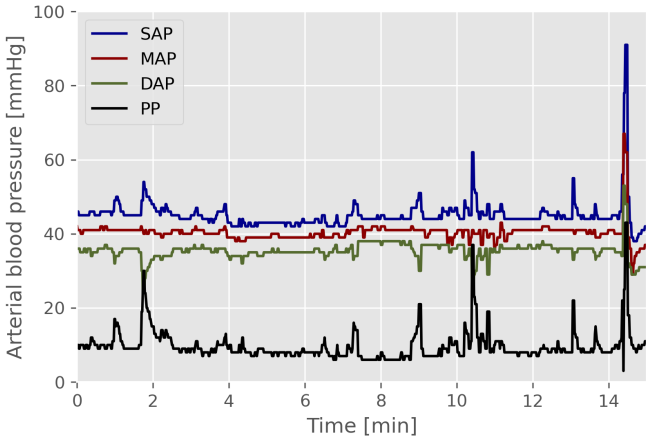


Figure 3: Recording showing an abrupt but brief increase of high magnitude in arterial blood pressure (ABP). Due to the abruptness, high magnitude and short duration, this is probably an artefact which could be caused by (accidental) manipulation of the measurement system. SAP, MAP, DAP = systolic, median and diastolic arterial pressure, respectively; PP = pulse pressure.

the preductal SpO_2 if both measurements were present in the data. When only one SpO_2 measurement was present in a data file, that was also assumed to be the preductal SpO_2 measurement.

The vital parameter data were processed by first removing all invalid data. After that, all data points and abrupt changes outside the range that were not considered physiologically possible (e.g. the artefacts in Figures 2 and 3) were also removed. These types of artefacts can be due to (accidental) manipulation of measurement systems, the administration of drugs, the withdrawal of blood, or zeroing of the arterial line. Other important sources of artefacts specifically in the ABP data are resonance, underdamping, and overdamping. [47, 48] It is assumed that resonance and underdamping artefacts are largely avoided by using catheters and tubing of appropriate length and stiffness or are removed otherwise by producing values outside the defined physiological limits (see Table 8). In order to detect periods of overdamping, a modified version of the algorithm of Cao et al. was used. [49] Around all detected artefacts, a margin of 5 seconds on each side was also removed to account for possible disturbances causing the artefact or actions taken to remove the cause of the artefact.

3.2.3 Mechanical ventilator data

In order to calculate OSI, the FiO_2 and $\tilde{P}_{aw}$ are also needed in addition to the preductal SpO_2 (see Equation 2). FiO_2 is a set value on the mechanical ventilator and the $\tilde{P}_{aw}$ is calculated by the mechanical ventilator based on the applied pressure over time. These values are stored in the patient's EHR with a variable sample frequency of around 1 sample per minute and extracted for the purpose of this study. With these values, the OSI was calculated according to Equation 2.

3.2.4 ECG recordings

One-lead ECG recordings (lead I or II), stored at a sample frequency of 200 Hz, were made continuously throughout the PICU stay of each patient. After extracting the 15-minute data window from the ECG data, the quality of the signal was assessed using an algorithm based on the method described by Zhao and Zhang. [50] Signals that were classified as unacceptable in quality were excluded from analysis. The R peaks were then detected using the Pan-Tompkins algorithm. [51] All ECG processing steps and the subsequent calculation of HRV measures were performed using the Python package *NeuroKit2*[1]. [52]

3.2.5 Calculation of predictors

Because normal distributions were not assumed, the median and interquartile range (IQR) were calculated for each 15-minute window to be used as predictors. This was only done if the window contained more than 80% valid

[1]For documentation of the *NeuroKit2* package, see https://neuropsychology.github.io/NeuroKit/

data points after processing. The only exception was when the amount of valid HR data within the window was below 80%, but the window contained 80% or more valid PLS data. In that case, PLS was used instead of HR. The median and IQR were not calculated for the HRV measures, as those predictors were already calculated over the complete 15-minute window.

3.3 Outcome variables

3.3.1 Cardiac ultrasounds

All patients underwent CUS within 24 hours after birth. During the PICU stay, additional CUS were performed upon indication or if required under participation in a clinical trial. All CUS were performed by trained paediatric cardiologists. Before the 2nd of March, 2021, the GE Vivid S6 (GE Healthcare, Chicago, IL, USA) was used to perform the CUS. After that date, the GE Vivid S60 was used. No specific study protocol was followed unless the patient was enroled in another study. The start of the CUS was defined by the timestamp of the CUS report. All timestamps of continuous data were synchronised on UTC by correcting for daylight saving time and for possible time differences between the CUS machine and the secure server containing the data.

Furthermore, because ECMO therapy has a significant influence on several cardiovascular and respiratory parameters, only CUS during which the patient did not receive ECMO therapy were used. Moreover, CUS performed more than 720 hours (30 days) after admission were also excluded from this study. This was because the neonatal period, defined as the first four weeks (28 days) of life, was of most interest here. The additional two days were included to prevent the exclusion of CUS just after 28 days which were performed a relatively long time after the preceding CUS.

3.3.2 Classification

Based on the CUS reports, a trained paediatric intensivist determined the degree of PH and CD according to the criteria in Table 1. If there was doubt as to which class to assign, a trained paediatric cardiologists was consulted. The classification of PH was based on the PAP in relation to systemic pressure. PAP is estimated using the pressure gradient over the tricuspid valve, the direction of the shunt over the ductus arteriosus (if still open), and the presence of dilation of the right ventricle and/or flattening of the IVS. Factors used for CD classification were fractional shortening, ventricle diameter, and reported professional evaluation by the paediatric cardiologist. The classes of PH and CD defined here are equal to the classification used in earlier studies. [10, 12] If no classification of PH and/or CD was possible due to insufficient measurements reported, that CUS was excluded.

Pulmonary Hypertension		**Cardiac Dysfunction**	
Criteria	**Class**	**Criteria**	**Class**
PAP $\leq \frac{2}{3}$ of systemic pressure	0	No dysfunction	0
PAP $> \frac{2}{3}$ of systemic pressure	1	Right ventricle dysfunction	1
and PAP $<$ systemic pressure		Left ventricle dysfunction	2
Suprasystemic PAP	2	Right and left ventricle dysfunction	3

Table 1: Criteria used for classification of pulmonary hypertension and cardiac dysfunction. Classification happened based on reports from cardiac ultrasounds. PAP = pulmonary artery pressure.

3.4 Ethics

This study was approved by the medical ethics committee of the Erasmus MC (MEC-2021-0937) under an overarching study protocol regarding the collection, storage, processing and analysis of data from the PICU of the Erasmus MC Sophia Children's Hospital.

4 | Statistical analyses

4.1 Dichotomisation of outcome variables

The proportions of patients in the CD classes 1 to 3 are known to be relatively low compared to the group without cardiac dysfunction (CD class 0). [7] Together with the fact that regression analyses with more than two outcome variables are more complex to perform and interpret, the PH and CD scores were dichotomise. The PH scores were divided into a group with no to moderate PH (class 0-1) and severe PH (class 2). For the CD scores, a group without CD (class 0) and a group with CD (classes 1-3) was used.

4.2 Data exploration and variable selection

Before analysis, the data were explored following a protocol published by Zuur et al. where applicable. [53] All data exploration and variable selection were performed using the R programming language (version 4.2.3) in the RStudio environment (version 2023.03.0) [54, 55]. An overview of the steps described in this section, including the model fitting and validation described in Sections 4.3 and 4.4, can be found in Figure 4.

First, Cleveland dot plots were made for all predictors in order to identify and exclude extreme outliers. [53] This was also done of the time from admission to each CUS. Furthermore, because the statistical model (see Section 4.3) groups the CUS per patient and expects each group to be equal in size, the difference in the number of CUS for each patient needed to be limited to reduce the relative number of data the model would have considered missing. The maximum number of CUS for each patient was set to be five. If a patient had more than five CUS, the CUS with the least number of calculated predictors was excluded, as those CUS would probably have contributed the least to the prediction of outcomes.

After removing outliers, the assumption of non-collinearity was tested, meaning that there should be no linear relationship between predictors. [56] In order to test for this assumption, the Pearson correlation coefficient was calculated for each pair of predictors. Two predictors were considered collinear if the absolute value of the correlation coefficient was 0.7 or higher. Furthermore, box plots were made of all predictors versus the outcome variables PH and CD to roughly assess the possible differences between the outcome variables. On the basis of these graphs, the correlation coefficients and knowledge of the pathophysiology of PH and CD in CDH, choices were made as to which predictors to remove from further analysis. This was done separately for the prediction of PH and CD and in cooperation with a paediatric intensivist and a technical physician.

Next, quantile-quantile plots (QQ-plots) were made of all remaining predictors and for each group of PH and CD in order to check the assumption for normality. Considering the presence of zero values in several predictors, the square root was calculated of the predictors that did not reasonably meet the assumption of normality. [57]

Finally, the variance inflation factor (VIF) was calculated for each remaining predictor. The VIF measures the relative inflation of the variance of the regression coefficient of each predictor due to collinearity. [56] If this relative inflation is high, the power of tests will be reduced. [58] Unlike a pairwise measure such as the Pearson correlation coefficient, the VIF is calculated based on the linear relationship between a predictor and all other predictors within a model. [59, 60] Using a sequential approach, the predictor with the highest VIF was excluded after which the VIF of the remaining values was recalculated. [53] This process was repeated until all VIF values were below 10, which is a threshold often used to consider the VIF as large. [56, 59]

4.3 Model fitting

For the prediction of the dichotomous outcome variables PH and CD, logistic mixed effects models (LMEM) were fitted. Mixed effects models can be used for data with a multilevel hierarchy, which is the case here since the CUS are often repeated within one patient. [61] Consequently, the PH and CD measurements are not independent. [58] With modelling the grouping factor at the patient level, the violation of the assumption of independence of the PH and CD measurements was accounted for. Due to the exploratory basis of this research and the difficulty of

interpretation, only the intercept of the grouping factor was modelled. For the same reason, no interactions were used in the models. [58] Before fitting, all predictors were centered around their mean and caution was taken to avoid common pitfalls of logistic regression. [62] All models were fitted using the R-based jamovi software (version 2.3.21). [63]

First, univariable LMEM were fitted to assess the predictive value of all separate predictors on the outcome variables, using a significance level of 0.05. Next, multivariable models were fitted for the prediction of PH and CD by performing a sequential forward selection procedure. The model fit criterion used for this procedure was the Akaike information criterion (AIC). The AIC is a measure of fit based on the maximised log-likelihood of a model, while penalising for the number of parameters. [61, 64] During the forward selection procedure, the first predictor to be included in the model is the predictors of which the univariable LMEM has the lowest AIC. Subsequently, predictors were included in the model based on which additional predictor produced the largest reduction in AIC. This process was repeated until no further reduction of the AIC was possible. Predictors were not included if their addition to the model caused the model not to converge or resulted in unlikely large increases in standard errors or coefficients. For each fitted model, odds ratios (OR) are calculated, defined as the probability that the outcome will occur divided by the probability that the outcome will not occur [65].

4.4 Model validation

In order to validate the LMEM, a leave-one-out cross-validation procedure (LOO-CV) was followed. During this procedure, the models were trained with all data except one observation. The model was then used to predict in which group of either PH or CD the remaining observation was classified. This was repeated until the classified group was predicted for all observations. LOO-CV results in a low bias compared to other cross-validation procedures and is less complex when dealing with large numbers of missing data. [66] Based on the results of the LOO-CV, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for each model.

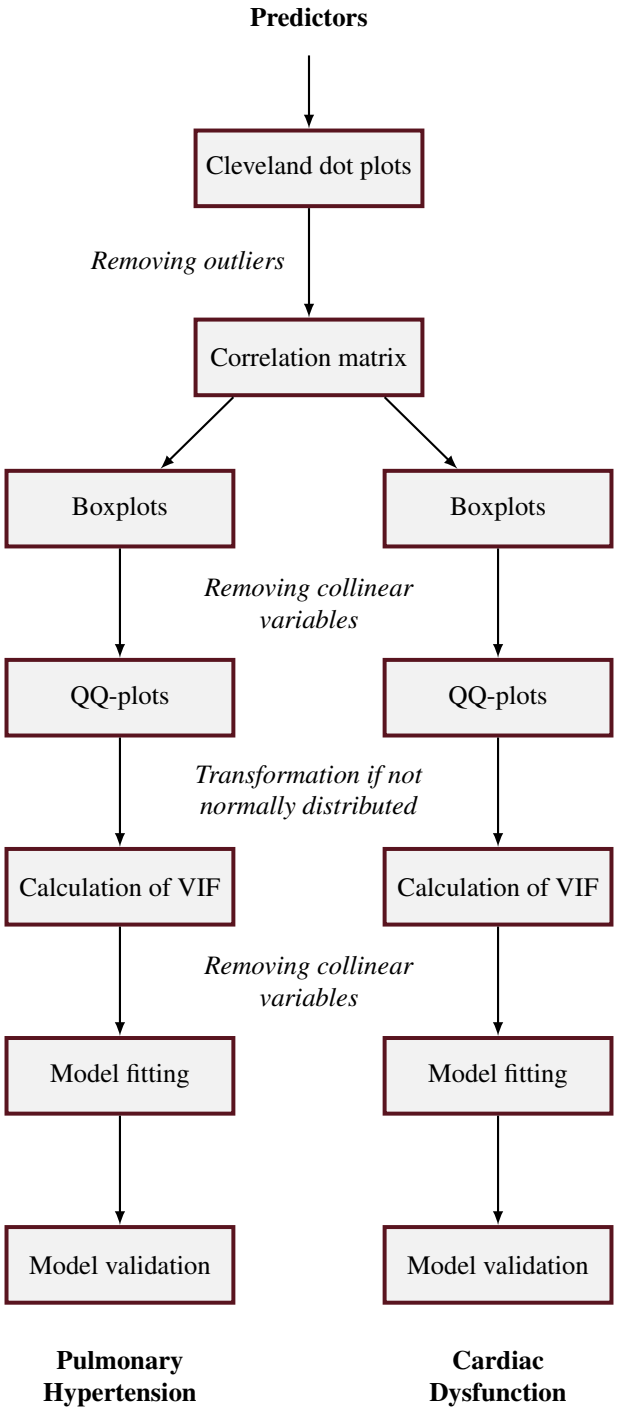


Figure 4: Flowchart of the data exploration and statistical analyses in this study. After creating the correlation matrix, the variables were analysed in two parallel paths: one for creating a model for the prediction of pulmonary hypertension and another for creating a model for the prediction of cardiac dysfunction. QQ-plots = quantile-quantile plots; VIF = variance inflation factor.

5 | Results

5.1 Patients

Between the 1st of January 2019 and the 31th of December 2022, 57 patients were admitted to the PICU of the Erasmus MC Sophia Children's Hospital for treatment of CDH. Of these patients, 19 patients (33.3%) required ECMO treatment for at least one period and 49 patients (86.0%) survived until discharge.

5.2 Continuous data

Of the vital parameters, only two files (1.5%) could not be retrieved. OSI could not be calculated for 39 CUS (28.7%) due to missing mechanical ventilator data. Of 48 CUS (35.8%), no ECG data was found and 11 ECG recordings (12.5%) were excluded from analysis due to unacceptable quality. Consequently, HRV measures were calculated for 77 CUS (57.5%). Two CUS (1.5%) had no valid measures and were completely excluded from the analysis. Extreme outliers were removed based on Cleveland dot plots, which can be found in Appendix B. An overview of the available parameters in total and per group of PH and CD can be found in Table 2. Due to the low numerical values, the HRV-VLF and the HRV-HF were both multiplied by 1000 to aid visualisation and to obtain more comparable ranges between the predictors.

		Pulmonary Hypertension		**Cardiac Dysfunction**	
Predictor	**CUS**	**Class 0-1**	**Class 2**	**Class 0**	**Class 1-3**
Total	*134 (100%)*	*76 (100%)*	*58 (100%)*	*72 (100%)*	*62 (100%)*
HR	131 (97.8%)	74 (97.4%)	57 (98.3%)	70 (95.9%)	61 (96.8%)
preductal SpO_2	123 (91.8%)	73 (96.1%)	50 (86.2%)	68 (94.4%)	55 (88.7%)
postductal SpO_2	55 (41.0%)	27 (35.5%)	28 (48.3%)	28 (38.9%)	27 (43.5%)
$dSpO_2$	53 (39.6%)	27 (35.5%)	26 (44.8%)	27 (37.5%)	26 (41.9%)
OSI	89 (66.4%)	48 (63.2%)	41 (70.7%)	47 (65.3%)	42 (67.7%)
ABP measures	101 (75.4%)	53 (69.7%)	48 (82.8%)	51 (70.8%)	50 (80.6%)
HRV measures	77 (56.7%)	47 (61.8%)	29 (50.0%)	44 (61.1%)	32 (51.6%)

Table 2: Number of cardiac ultrasounds (CUS) for each type of predictor in total and for each group of pulmonary hypertension and cardiac dysfunction. This only includes CUS during which the patient did not receive extracorporeal membrane oxygenation therapy. HR = heart rate; SpO_2 = peripheral oxygen saturation; $dSpO_2$ = difference between preductal and postductal SpO_2; OSI = oxygen saturation index; ABP = arterial blood pressure, of which the pulse pressure and systolic, mean and diastolic arterial pressure are components; HRV = heart rate variability.

5.3 Outcome variables

A total of 167 CUS were performed, of which 134 CUS (80.2%) were performed without the patient receiving ECMO therapy and of which both the PH and CD classes could be scored. The median number of CUS per patient was 2 [range 1-7]. Three CUS were excluded to obtain a maximum of five CUS per patient. No outliers were identified based on the Cleveland dot plot of the time from admission to CUS (see Appendix B). The classification of all CUS without simultaneous ECMO, before dichotomisation, can be seen in Table 3.

	Classification			
	Class 0	**Class 1**	**Class 2**	**Class 3**
Pulmonary Hypertension	32	44	58	-
Cardiac Dysfunction	72	54	0	8

Table 3: Number of cardiac ultrasounds (CUS) per class of pulmonary hypertension and cardiac dysfunction for all CUS during which the patient did not receive extracorporeal membrane oxygenation therapy.

5.4 Variable selection and transformation

Based on the correlation matrix of the Pearson correlation coefficients of each pair of predictors and the boxplots (see Figure 6 and Appendix C, respectively), the median of the postductal SpO_2, DAP and SAP; the IQR of the preductal SpO_2, postductal SpO_2, PP, DAP and OSI; and the HRV-LF and HRV-LFn were excluded to remove collinearities within the data.

The median of postductal SpO_2 and $dSpO_2$ showed similar differences between the PH and CD groups in the boxplots. $dSpO_2$ was considered more informative for PH than postductal SpO_2 as $dSpO_2$ is not influenced by shunting across the foramen ovale or pulmonary factors. Consequently, the median of the postductal SpO_2 was excluded. Because the median values of SAP, MAP, DAP, and PP show similar differences between the PH and CD groups and because MAP is more often used in clinical practice, the median of MAP was chosen instead of the median of DAP or SAP. This was done for the prediction of both PH and CD. Consequently, the median of PP was also kept for further analysis due to its correlation with the median of SAP. Furthermore, of the IQR predictors, only the postductal SpO_2 and SAP showed a slight difference between the PH and CD groups. Due to the high percentage of missing values, it was decided to exclude the IQR of the postductal SpO_2 together with all other correlated IQR predictors without an apparent effect on the box plots. For the HRV predictors, the selection was based solely on the box plots, since it is unclear whether and how the power in the low-frequency band or

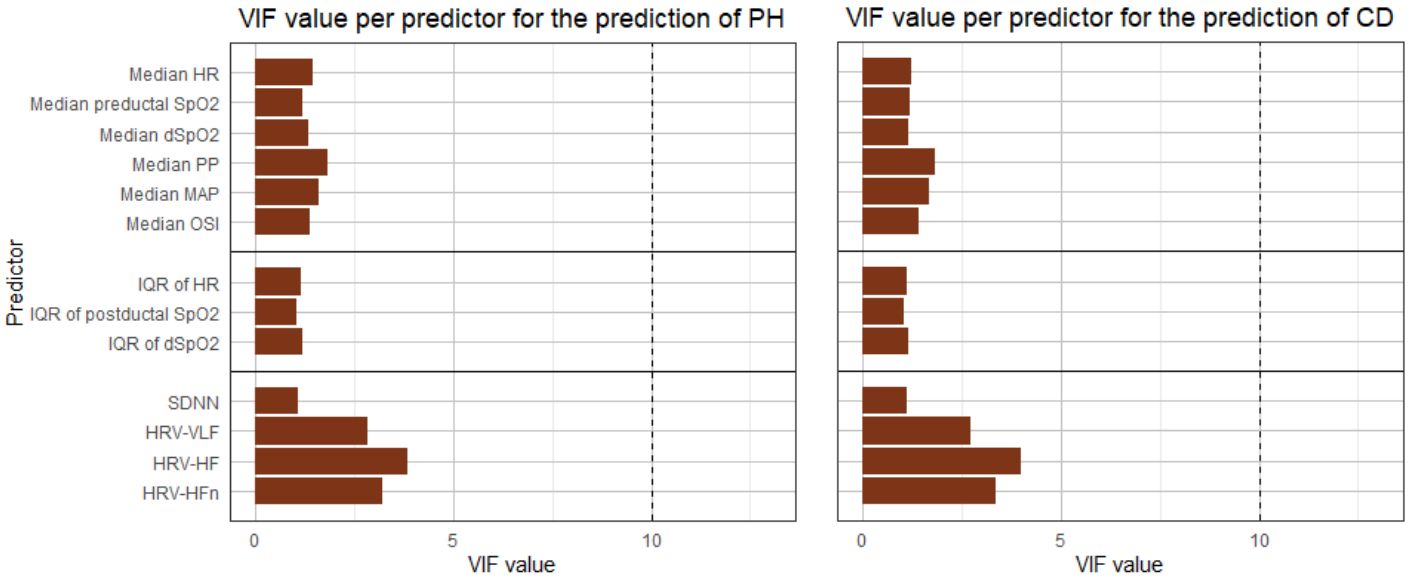


Figure 5: Bar charts of the variance inflation factors (VIF) per predictor for the prediction of pulmonary hypertension (PH) and cardiac dysfunction (CD). The VIF values are calculated after fitting three separate generalised linear models for the median, interquartile range (IQR) and heart rate variability (HRV) predictors. It was not possible to fit all predictors into one model due to the high percentage of missing values. HR = heart rate; SpO_2 = peripheral oxygen saturation; $dSpO_2$ = difference between preductal and postductal SpO_2; PP = pulse pressure; MAP = mean arterial pressure; OSI = oxygen saturation index; SDNN = standard deviation of the normal-to-normal beat intervals; HRV-VLF and HRV-HF = total spectral power of heart rate variability in the very low and high frequency bands, respectively; HRV-HFn = HRV-HF normalised to the total power.

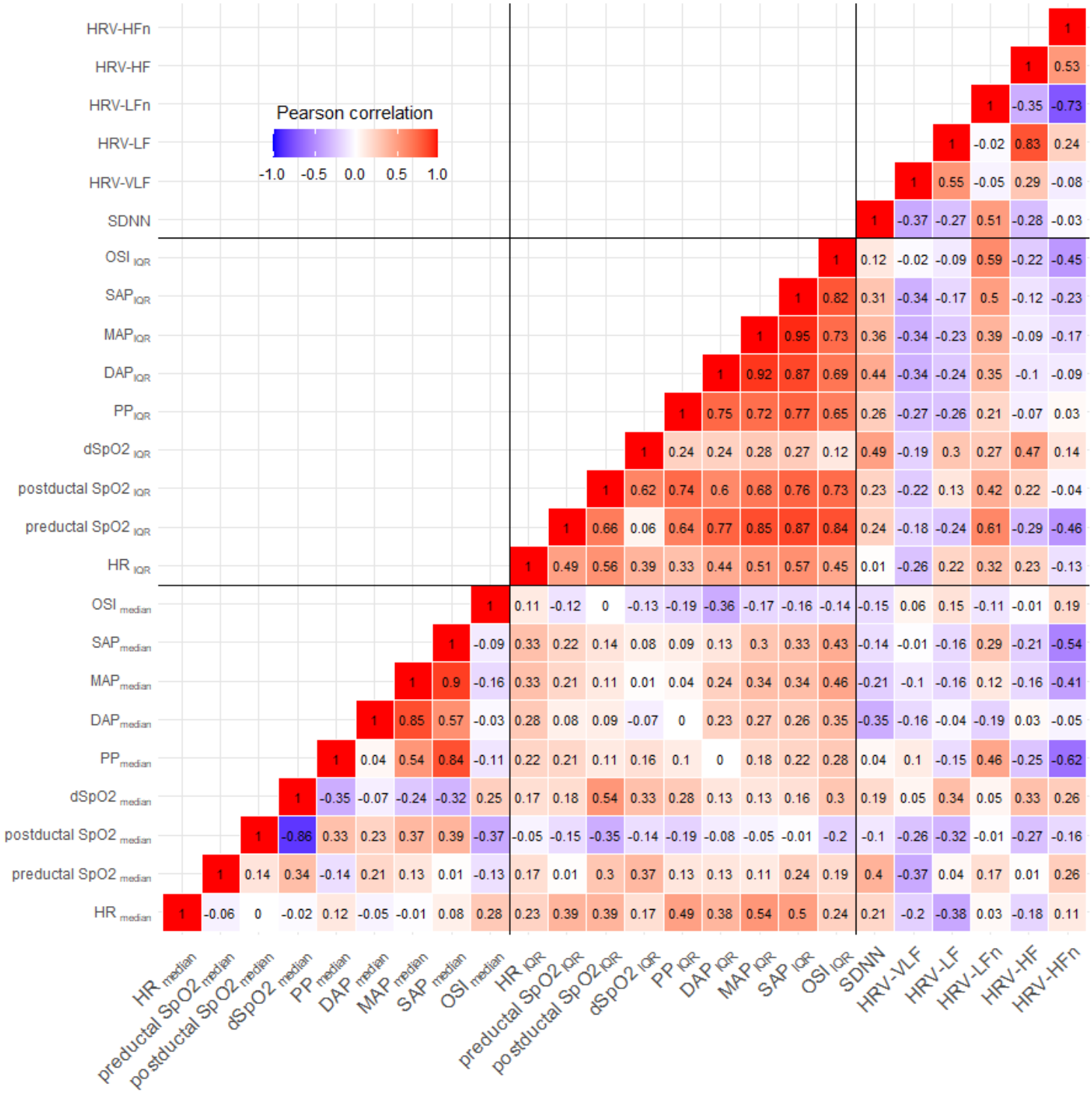


Figure 6: Correlation matrix containing the Pearson correlation coefficient of each pair of predictors. The colour indicates the direction and magnitude of each correlation. The subscripts indicate the type of predictor (median or interquartile range (IQR)). Pairs with a correlation coefficient higher or equal than 0.70 or lower or equal than -0.70 were considered correlated to each other. The black lines separate the different types of predictors as a visual aid. HR = heart rate; SpO_2 = peripheral oxygen saturation; $dSpO_2$ = difference between preductal and postductal SpO_2; PP = pulse pressure; DAP, MAP and SAP = diastolic, mean and systolic arterial pressure, respectively; OSI = oxygen saturation index; SDNN = standard deviation of the normal-to-normal beat intervals; HRV-VLF, HRV-LF and HRV-HF = total spectral power of heart rate variability in the very low, low and high frequency bands, respectively; HRV-LFn and HRV-HFn = HRV-LF and HRV-HF normalised to the total power, respectively.

the power in the high-frequency band might be related to PH or CD. Because HRV-HFn appeared to be more promising for the prediction of both PH and CD, it was preferred over HRV-LFn. Lastly, because only a slight difference was observed between the PH classes for HRV-HF but not HRV-LF and no differences were observed between the CD groups for those predictors, HRV-HF was selected for the prediction of both PH and CD.

Next, the IQR of HR, SDNN, HRV-VLF and HRV-HF were squared because of their skewed distribution. The QQ-plots of all predictors can be found in Appendix D. After normalisation, the VIF was calculated for each predictor. Due to the presence of a significant number of missing values, it was not possible to fit one simple linear model to calculate the VIF values. Unlike LMEM, a linear model drops all observations with missing values, which would have resulted in an insufficient number of CUS to create a model based on which the VIF values could be calculated. With less variables, less observations were dropped. Because collinearity was most expected in similar predictors, the VIF values were calculated using three different models for the three types of predictors (median, IQR and HRV). The VIF values for these three groups for the prediction of both PH and CD can be found in Figure 5. Because none of the VIF values exceeded 10, additional exclusions of predictors were not needed.

5.5 Univariable models

In Table 4, the OR values of both the intercept and the coefficient of each univariable LMEM can be found, including 95% confidence intervals (CI). For the prediction of PH, the OR values of both the median and the IQR of the HR are statistically significant. Furthermore, statistically significant OR values were also found for the median values of preductal SpO_2, $dSpO_2$, PP and OSI. In the univariable LMEM for the prediction of CD, the HRV-VLF and the median values of HR, MAP and OSI were statistically significant. Except for the models for HRV-HF and HRV-HFn, no intercept value reached statistical significance. The performance measures of all univariable LMEMs that achieved statistical significance can be found in Table 5.

Predictor	**N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
			Pulmonary Hypertension		
Median of HR	131	50.0%	75.3%	60.9%	66.3%
Median of preductal SpO_2	123	30.6%	84.7%	57.7%	64.2%
Median of $dSpO_2$	53	50.0%	85.2%	76.5%	63.9%
Median of PP	101	53.2%	58.8%	54.3%	57.7%
Median of OSI	89	62.5%	81.3%	73.5%	72.2%
IQR of HR	131	60.7%	65.8%	57.6%	68.6%
			Cardiac Dysfunction		
Median of HR	131	40.7%	70.0%	53.3%	58.3%
Median of MAP	101	54.2%	51.0%	51.0%	54.2%
Median of OSI	89	48.8%	72.3%	60.6%	61.8%
HRV-VLF	73	44.8%	84.1%	65.0%	69.8%

Table 5: Performance measures of all statistically significant univariable logistic mixed effects models. All predictors were centered around the mean. N = number of observations; PPV = positive predictive value; NPV = negative predictive value; HR = heart rate; SpO_2 = peripheral oxygen saturation; $dSpO_2$ = difference between preductal and postductal SpO_2; PP = pulse pressure; OSI = oxygen saturation index; IQR = interquartile range; MAP = mean arterial pressure.

Predictor	Mean	Unit	Intercept			Coefficient		
			OR	95% CI	p-value	OR	95% CI	p-value
			Pulmonary Hypertension					
Median predictors								
HR	153	bpm	0.741	0.502 - 1.090	0.131	1.035	1.014 - 1.060	0.001*
preductal SpO_2	96.3	%	0.691	0.428 - 1.115	0.130	0.753	0.630 - 0.901	0.002*
$dSpO_2$	3.91	%	1.150	0.486 - 2.720	0.750	1.290	1.009 - 1.640	0.042*
MAP	45.8	mmHg	0.894	0.591 - 1.350	0.596	0.935	0.874 - 1.000	0.052
PP	22.1	mmHg	0.909	0.593 - 1.395	0.663	0.927	0.872 - 0.985	0.015*
OSI	8.04	1	0.850	0.518 - 1.400	0.521	1.302	1.126 - 1.500	<0.001*
IQR predictors								
HR	1.42	$\sqrt{\text{bpm}}$	0.699	0.445 - 1.098	0.120	0.343	0.182 - 0.648	<0.001*
$dSpO_2$	0.887	%	0.965	0.553 - 1.690	0.901	1.166	0.815 - 1.670	0.400
SAP	2.9	mmHg	0.921	0.620 - 1.370	0.686	0.948	0.758 - 1.180	0.637
HRV predictors								
SDNN	2.41	$\sqrt{\text{ms}}$	0.639	0.386 - 1.060	0.081	0.633	0.164 - 2.440	0.507
HRV-VLF	1.71	$\sqrt{1000 \cdot \text{ms}^2}$	0.583	0.361 - 0.941	0.027*	0.813	0.511 - 1.295	0.384
HRV-HF	2.53	$\sqrt{1000 \cdot \text{ms}^2}$	0.590	0.367 - 0.947	0.029*	1.156	0.928 - 1.441	0.196
HRV-HFn	0.314	nu	0.610	0.382 - 0.975	0.039*	5.148	0.347 - 76.36	0.234
			Cardiac Dysfunction					
Median predictors								
HR	153	bpm	0.843	0.546 - 1.300	0.440	1.021	1.001 - 1.040	0.045*
preductal SpO_2	96.3	%	0.801	0.527 - 1.220	0.298	0.931	0.846 - 1.020	0.144
$dSpO_2$	3.91	%	0.993	0.534 - 1.850	0.982	1.098	0.984 - 1.230	0.093
MAP	45.8	mmHg	0.911	0.559 - 1.483	0.707	0.923	0.855 - 0.996	0.040*
PP	22.1	mmHg	0.943	0.591 - 1.500	0.804	0.965	0.910 - 1.020	0.234
OSI	8.04	1	0.873	0.546 - 1.400	0.572	1.151	1.031 - 1.280	0.012*
IQR predictors								
HR	1.42	$\sqrt{\text{bpm}}$	0.833	0.544 - 1.280	0.402	0.686	0.433 - 1.090	0.109
$dSpO_2$	0.887	%	0.970	0.545 - 1.730	0.918	1.139	0.788 - 1.650	0.489
SAP	2.9	mmHg	0.953	0.611 - 1.490	0.831	1.010	0.798 - 1.280	0.937
HRV predictors								
SDNN	2.41	$\sqrt{\text{ms}}$	0.690	0.372 - 1.280	0.239	5.868	0.904 - 38.10	0.064
HRV-VLF	1.71	$\sqrt{1000 \cdot \text{ms}^2}$	0.593	0.326 - 1.079	0.087	0.543	0.312 - 0.942	0.030*
HRV-HF	2.53	$\sqrt{1000 \cdot \text{ms}^2}$	0.676	0.391 - 1.170	0.161	1.022	0.806 - 1.300	0.858
HRV-HFn	0.314	nu	0.703	0.411 - 1.200	0.197	2.848	0.167 - 48.44	0.469

Table 4: Univariable logistic mixed effects models for the prediction of either pulmonary hypertension or cardiac dysfunction. All predictors were centered around the mean. The odds ratio (OR) was calculated as e^{β} with β the intercept or coefficient value. Before fitting, IQR of HR and SDNN were squared and HRV-VLF and HRV-HF were multiplied with 1000 and then squared. CI = confidence interval; HR = heart rate; SpO_2 = peripheral oxygen saturation; $dSpO_2$ = difference between preductal and postductal SpO_2; PP = pulse pressure; MAP = mean arterial pressure; OSI = oxygen saturation index; SDNN = standard deviation of the normal-to-normal beat intervals; HRV-VLF and HRV-HF = total spectral power of heart rate variability in the very low and high frequency bands, respectively; HRV-HFn = HRV-HF normalised to the total power; nu = normalised units.

5.6 Multivariable models

The course of the forward selection process is described in Table 6. For the prediction of PH, this process resulted in a multivariable LMEM with the SDNN and the median values of $dSpO_2$, HR, PP and OSI as predictors (see Table 7). The LOO-CV for this model was performed with 20 complete observations of which 10 CUS were classified as PH classes 0-1 and 10 CUS as PH class 2. The model showed a sensitivity of 72.0%, a specificity of 80.0%, a PPV of 77.8%, and an NPV of 72.7%. The LMEM for the prediction of CD consisted of the median $dSpO_2$, the HRV-VLF, the SDNN and the IQR of SAP as predictors. The LOO-CV was performed with 21 complete observations of which 13 CUS were classified as CD class 0 and 8 CUS as CD classes 1-3. The model showed a sensitivity of 62.5%, a specificity of 76.9%, a PPV of 62.5%, and an NPV of 76.9%.

Pulmonary Hypertension		**Cardiac Dysfunction**	
Predictors	**AIC**	**Predictors**	**AIC**
Median of $dSpO_2$	66.22	Median of $dSpO_2$	75.68
+ HRV-SDNN	35.71	+ HRV-VLF	31.79
+ Median of HR	33.89	+ HRV-SDNN	29.17
+ Median of PP	29.87	+ IQR of SAP	23.31
+ Median of OSI	28.33		

Table 6: Description of the forward selection procedure for creating the multivariable logistic mixed effects models for the prediction of pulmonary hypertension and cardiac dysfunction. The selection criterion for the forward selection procedure was the Akaike information criterion (AIC), which was minimised. $dSpO_2$ = difference between preductal and postductal peripheral oxygen saturation; SDNN = standard deviation of the normal-to-normal beat interval; HR = heart rate; PP = pulse pressure; OSI = oxygen saturation index; HRV-VLF = total spectral power of heart rate variability in the very low frequency band; IQR = interquartile range; SAP = systolic arterial pressure.

Predictor	**Mean**	**Unit**	**OR**	**95% CI**	**p-value**
			Pulmonary Hypertension		
Intercept	-	-	1.068	0.222 - 5.140	0.935
Median of $dSpO_2$	3.91	%	1.281	0.934 - 1.760	0.125
SDNN	2.41	$\sqrt{\text{ms}}$	0.217	0.001 - 40.56	0.567
Median of HR	153	bpm	1.073	0.988 - 1.170	0.094
Median of PP	22.1	mmHg	0.879	0.749 - 1.030	0.114
Median of OSI	8.04	1	1.174	0.742 - 1.860	0.494
			Cardiac Dysfunction		
Intercept	-	-	0.451	0.068 - 3.000	0.410
Median of $dSpO_2$	3.91	%	1.709	0.966 - 3.020	0.066
HRV-VLF	1.71	$\sqrt{1000 \cdot \text{ms}^2}$	0.017	0.000 - 1.090	0.055
SDNN	2.41	$\sqrt{\text{ms}}$	4.442	0.096 - 204.9	0.446
IQR of SAP	2.9	mmHg	0.621	0.285 - 1.350	0.230

Table 7: Multivariable logistic mixed effects models for the prediction of pulmonary hypertension and cardiac dysfunction. All predictors were centered around the mean. The odds ratio (OR) was calculated as e^{β} with β the intercept or coefficient value. CI = confidence interval; $dSpO_2$ = difference between preductal and postductal peripheral oxygen saturation; SDNN = standard deviation of the normal-to-normal beat interval; HR = heart rate; PP = pulse pressure; OSI = oxygen saturation index; HRV-VLF = total spectral power of heart rate variability in the very low frequency band; IQR = interquartile range; SAP = systolic arterial pressure.

6 | Discussion

6.1 Relevance

Although there are similar studies on the predictive value of vital and clinical parameters in CDH, most of these studies focused on the prediction of mortality or other overall outcomes. [11, 20, 25, 26, 28, 29] Moreover, the current method of assessing the degree of PH and CD through CUS is relatively labour-intensive and often experienced as stressful for these critically ill patients. [10, 12] Consequently, CUS are only performed when deemed necessary based on other clinical indicators, often resulting in intervals of days or even more between subsequent CUS. Continuously and non-invasive measured parameters that predict the degree of PH and CD can help guide bed-side treatment and allow monitoring of subsequent treatment effects. It is likely that with more timely interventions, (further) increases in the degree of PH and/or CD can be mitigated or even prevented. Conversely, the length of stay of patients may even be reduced by earlier detection of improvement and facilitation of recovery.

This study fills an important gap within the existing literature by identifying continuously and non-invasively measured parameters that can be used to predict the concurrent degree of PH and CD in neonates with CDH. One study did look at the prediction of PH in CDH using the mean OSI value in the first hour and the maximum OSI values in the first 12 and 24 hours after birth. [33] However, the mean OSI value in the first hour after birth was used more as a prognostic factor rather than as a predictor of concurrent degree of PH. Moreover, maximum OSI values are not suited for long-term monitoring purposes. No studies have attempted to predict CD in patients with CDH using continuously measured parameters.

6.2 Prediction of pulmonary hypertension

Several continuously measured parameters have been shown to be associated with the degree of PH. The most promising results were found in the parameters related to oxygen saturation. As expected, patients with severe PH are more likely to have a lower preductal SpO_2, a higher $dSpO_2$ (i.e. right-to-left shunting across the ductus arteriosus) and a higher OSI (i.e. higher ventilation settings and/or lower preductal SpO_2). This is also expected since in a PICU, the preductal SpO_2 can often be maintained at values close to 100% until the point when the patient's pulmonary condition becomes severe. In earlier studies, it has already been shown that there is a relationship between OSI values within the first 24 hours after birth and PH. [33] Other studies in CDH found associations between preductal SpO_2, similar parameters such as OI and PaO_2 and survival. [20, 25, 26, 28, 29] Considering the fact that PH is also related to mortality, these studies may have looked at the same mechanisms that underlie the results found here. [10, 11] Although the sensitivity of the median preductal SpO_2, $dSpO_2$ and OSI were around or even far below chance in this study, these predictors have specificity values greater than 80% and the PPV values for the median values of $dSpO_2$ and OSI were 76.5% and 73.5%, respectively. Thus, within clinical practice, these parameters could be used to confirm a favourable pulmonary status or to initiate further diagnostics.

In addition, an increase in the median HR and a decrease in the IQR of HR appeared to increase the risk of severe PH, albeit with limited predictive performance. The highest performance measure of the two HR predictors was obtained for the median HR, with a specificity of 75.3%. When considering that the IQR of HR could also be seen as a HRV measure, these results are in agreement with the predictive value of SDNN in the multivariable LMEM and with previous studies reporting higher mean HR and lower HRV indices in adult patients with PH compared to healthy controls. [67, 68] However, it is inconsistent with the fact that none of the HRV predictors were statistically significant in the univariable LMEM for the prediction of PH. The median PP also reached statistical significance in the univariable LMEM. This can be explained by the fact that PP is dependent on left ventricular preload, which is reduced in PH. [69, 70]

The multivariable LMEM for the prediction of PH contained the SDNN and the median values of $dSpO_2$, HR, PP and OSI. With the exception of SDNN, all of these predictors also showed a statistically significant result in the univariable LMEM, with similar OR values. The inclusion of SDNN is again in line with previous findings

showing lower HRV values in adult patients with PH. [67, 68] All performance measures of this model were greater than 70%, with a specificity of 80% as the highest measure. Although that might not be sufficient for direct clinical application, these results are promising nonetheless.

6.3 Prediction of cardiac dysfunction

The median values of HR, MAP and the HRV-VLF were all independently predictive of CD, with higher chances of CD for increased median values of HR and OSI and decreased median MAP and HRV-VLF. No studies have been found that confirm the direct relationship between HR and CD in CDH, but CD is known to lead to hypotension in CDH. [3] An increase in HR might be a compensatory reaction to the decrease in stroke volume caused by CD. Additionally, the inclusion of HRV-VLF in the model is in line with a study that has shown that HRV-VLF is predictive of death or readmission in adult patients with congestive heart failure. [71] Moreover, it has also been shown that adult patients with subacute coronary artery disease have lower HRV-VLF values compared to healthy controls. [72] However, another study in neonates and infants with cardiac disease did not find a statistically significant result for HRV-VLF but did find HRV-HF to be predictive of impending cardiac arrest, which did not reach statistical significance here. [34] Thus, although conflicting results are found in the literature, HRV-VLF might be related to the occurrence and/or severity of CD.

Another interesting finding was that the median OSI, a marker of respiratory failure, was predictive of CD. Almost all cases of CD were classified as right ventricle dysfunction (see Table 3), which is usually secondary to PH in CDH. [7] With OSI predictive for PH, the predictive value of OSI for CD is then easily explained. It would be interesting to specify the effect of left ventricular and biventricular failure on the different parameters. However, the numbers of patients with these types of CD were too low to do so with these data. Unfortunately, most performance measures of the univariable LMEM for the prediction of CD did not exceed 60% or even had values below chance. The highest performance values were of the median of HR and OSI and the HRV-VLF with specificity values of 70.0%, 72.3% and 84.1%, respectively. Consequently, these predictors might be primarily useful in identifying CDH patients without CD.

In the multivariable LMEM for the prediction of CD, the median $dSpO_2$, HRV-VLF, SDNN and the IQR of SAP were included. Of these predictors, only HRV-VLF was also statistically significant in the univariable LMEM. Similar to why OSI might be predictive of CD, the presence of median $dSpO_2$ in the model can be explained through its relationship with PH and CD being often secondary to PH. Interestingly, the SDNN has an OR value greater than 1, which is in contrast with the OR value of below 1 for the prediction of PH and with what would be expected based on the literature. Namely, mortality was predicted by a lower SDNN in adult patients with heart failure. [73–75] In children with congenital heart disease, SDNN was correlated with the New York Heart Association (NYHA) functional class. [76]. However, a recent study found mean SDNN values close to 30 ms for healthy neonates, while the mean SDNN found here was 5.81 ms. [77] This would either mean that the SDNN of neonates with CDH is significantly lower than in healthy neonates, for which no explanation can be found at this time, or that the SDNN was incorrectly calculated. Further research should shed more light on the origins of these findings.

Next, the predictive value of the IQR of SAP could be explained by a reduced preload of the left ventricle and/or restricted left ventricular filling due to displacement of the interventricular septum. [12] In contrast, increased variability in systolic blood pressure has been known to have predictive and prognostic value of heart failure in adults. [78, 79] Additionally, mechanical ventilation also has an effect on arterial pressure variation through a decrease in venous return to the right ventricle, causing a reduction in the preload of the left ventricle and, consequently, stroke volume and SAP variability. [80, 81] In patients with CD, these ventilator effects may be reduced due to a different pressure distribution in the thorax caused by the pulmonary hypoplasia and the diaphragm defect. Therefore, it would be interesting to study the effects of mechanical ventilation on ABP variations in CDH patients. The highest performance measures of this model were specificity and NPV with a value of 76.9% for both measures. Consequently, although this model could be used to identify patients without CD, clinical use is limited at this time.

6.4 Limitations

The present study is not without limitations, although they have been mitigated as much as possible. First, the fact that this was a retrospective study caused several problems in data acquisition and analysis. With the exception

of the first CUS of each patient, most CUS were performed based on clinical indication rather than prescribed by a protocol. This resulted in an over-representation of patients whose clinical status was relatively unstable. Additionally, CUS reports often did not contain specific parameters needed for the classification of PH or CD. Consequently, classification of the degrees of PH and CD was regularly done with limited information. Also, CUS is not the golden standard to be used for the diagnosis of PH. The gold standard is cardiac catheterisation, which is not possible in this population of severely ill patients. In addition, almost all patients will show PH to some degree during the first CUS. Even in healthy neonates, the mean PAP gradually drops to 50% of systemic pressure at the end of the first day of life. [49] It may therefore be difficult, if not impossible, to distinguish physiological from pathological PH during this period. Because the majority of CUS were performed within the first day of life, the statistical power of the LMEM predicting PH will have been limited.

Another issue with respect to the data is the sampling frequency of 200 Hz of the ECG recordings. Namely, higher sampling frequencies of 250 to 500 Hz or even higher are recommended for the correct calculation of HRV measures. [38–40] A sampling frequency of 200 Hz might be sufficient when the RR interval variability is sufficiently high and the amplitude of the respiratory sinus arrhythmia (RSA) is low. RSA refers to HR accelerations and decelerations caused by respiration, mediated by the vagus nerve. [40] Within this study, it was assumed that RR variability was sufficiently high and that RSA did not play a significant role. However, RSA was observed in neonates in previous studies and contributed more than 30% to the frequency spectrum of HRV. [82, 83] Consequently, the HRV calculations may have been biased.

Furthermore, 91.8% of the CUS had a corresponding window with valid SpO_2 data, while only 41.0% of these CUS had a valid second SpO_2 measurement. This was due to a registration error in the years before 2020. Furthermore, the registration of the preductal and postductal SpO_2 measurements depends on which channel the oximeter physically connects to. Misconnections of the oximeters leads to a loss of either or both SpO_2 data. Generally, the postductal SpO_2 will have been missing. Missing preductal SpO_2 values may have biased OSI calculation, as OSI values calculated using postductal SpO_2 values are generally lower. Together with the fact that other parameters also often contained missing data, this could have led to statistical analyses being underpowered. Although these missing data could have been imputated, the choice was made not to do this due to the exploratory nature of this study and because most missing data were assumed not to be missing at random.

With regard to the statistical analyses, one limitation was the fact that no diagnostics were done on the LMEM after fitting. Consequently, it is unclear whether appropriate models were used and if other possible random effects should have been used, such as age or whether the patient was mechanically ventilated. Especially age could be relevant as HR, ABP and HRV values change during the first days and weeks of life, which has not been taken into account. [84–86] Additionally, the choice was made to exclude collinear variables from all further analyses, including the univariable analyses. Although this was done with the creation of a multivariable model in mind, this could have caused the exclusion of predictors that might have been independently predictive of PH or CD. This could, in turn, have influenced the choices made in the creation of the multivariable LMEM. Furthermore, there was an over-representation of PH class 2 within the LOO-CV due to the fact that only complete observations could be used. However, the over-representation was limited.

6.5 Future research

In order to draw stronger conclusions about the predictive value of specific parameters for the degree of PH and CD, a prospective trial is needed with specific focus for correct measurement and data registration and during which all patients will receive protocol-based CUS at predetermined points. Such a trial will improve the classification of PH and CD and give a more accurate representation of the patient population. Moreover, it will reduce the number of missing data, which will improve the power of the statistical analyses. The statistical method itself might be improved by incorporating interaction effects of variables and by taking the age and age-related changes in HR, ABP and HRV into account. [84–86] It is unknown whether these changes are relevant to the prediction of PH and/or CD, but it might be useful to investigate. Furthermore, the decision boundary within the LMEM to decide which PH or CD group a CUS belonged to was set at 50%, but this might not be the ideal cutoff point. Other decision boundaries could improve the prediction of PH and CD.

In addition, dichotomous outcome variables naturally do not correctly represent the diversity of severity of PH and CD within the patient population. The use of non-dichotomous outcome variables would provide a more

complete representation of the diversity of PH and CD severity. This can be done using discrete groups such as the classes used before dichotomisation, but there might also be a role here for continuous outcome variables. Although no literature on continuous measures of PH or CD was found, one might think that a measure such as the ratio of PAP to systemic pressure could be informative of the degree of PH. Lastly, considering the purpose of monitoring, it might be interesting to perform trend analysis of both continuous data and PH and CD measures and assess the similarity between those signals. An example of such an approach has been described by Henriques et al., who performed trend analyses on telemonitoring data and used a similarity measure to predict heart failure decompensation events. [87]

Furthermore, it might also be useful to combine continuously measured parameters with discrete measurements such as blood gas values or biomarkers such as brain-type natriuretic peptide (BNP) to gain a more complete impression of pulmonary and/or cardiac functioning. BNP has already been shown to predict PH in CDH and also correlates with right ventricular strain. [88, 89] However, an important condition for the use of such additional measurements would be that stable values over the course of hours can reasonably be assumed. This is because rapidly changing parameters could give a false impression of the general pulmonary and/or cardiac status of the patient between discrete measurements.

Lastly, some potential predictors that were identified in the preliminary literature review were not included in this study because they were simply not measured in our PICU. [30] CVP, for example, has been shown to predict of PH in adult patients with acute respiratory distress syndrome. [90] The downside of CVP measurements is that it is an invasive measurement which is often not performed in CDH patients. Another potentially useful parameter is the cardiac index, which might be used as a measure for cardiac functioning for which continuous and non-invasive measurement techniques exist. [91–94]

7 | Conclusions

This research aimed to identify continuously measured parameters predictive of the concurrent degree of PH and CD in neonates with CDH. These results show that the most promising predictive measures of PH are the median values of preductal SpO_2, $dSpO_2$ and OSI. For the prediction of CD, HRV-VLF and the median values of HR, OSI and $dSpO_2$ are the most promising predictors. Despite limited predictive performance of the regression models, these results contributes to improved monitoring of CDH patients, which can lead to more timely interventions and eventually improved outcomes within this patient population.

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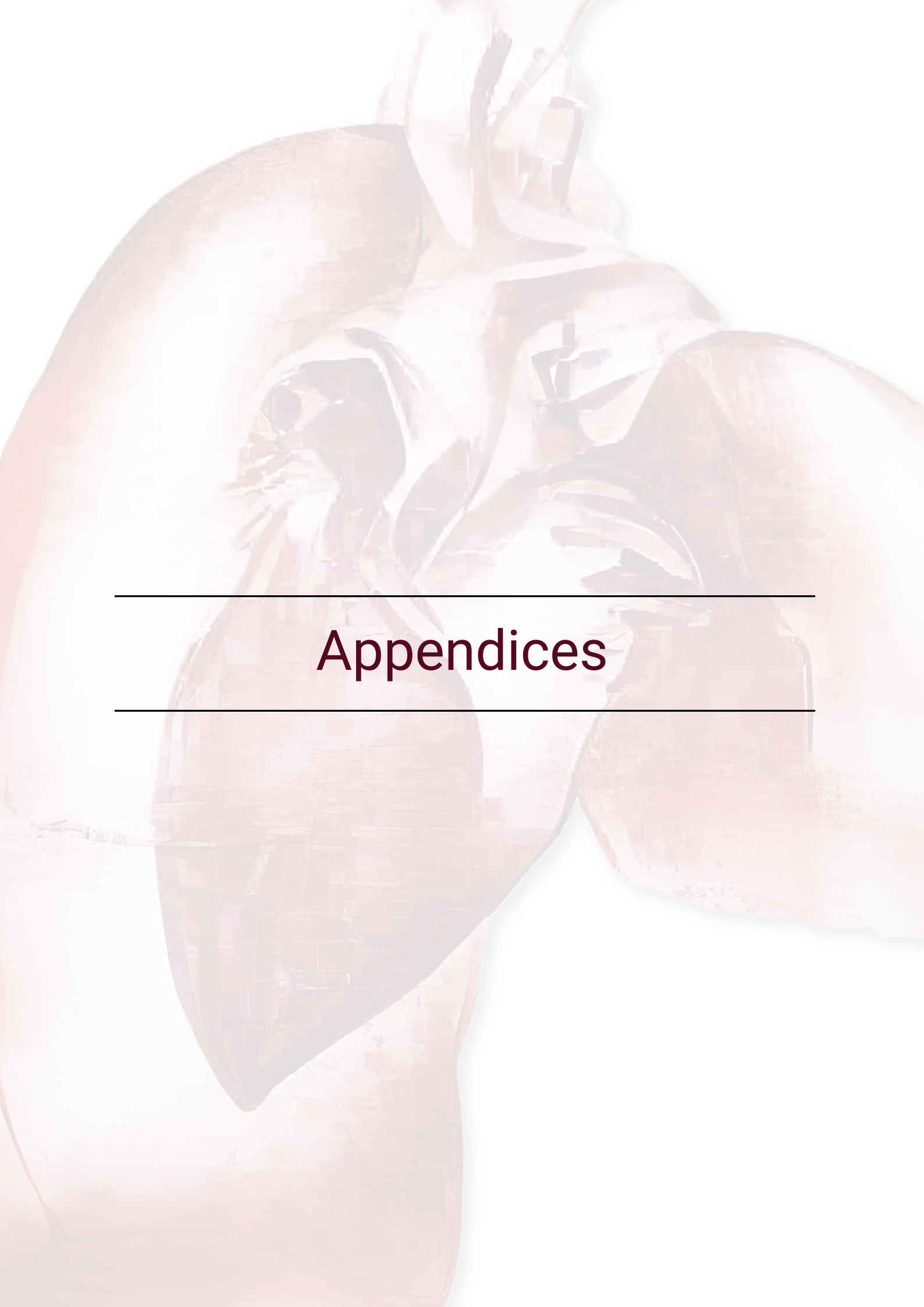

Appendices

A | Artefact detection and removal

A.1 Invalid data

All missing and invalid data points within the raw vital parameter data were removed in order to convert the data to numerical values and to preserve the structure of the data window. The same was done for HR data which were classified by the monitor as ventricular fibrillation or asystole. Furthermore, for all measured parameters, with the exception of $dSpO_2$, zero values were also considered artefacts and removed. This was not done for $dSpO_2$ as preductal and postductal SpO_2 are equal in the absence of shunting. An example of a recording with invalid ABP data can be seen in Figure 7.

A.2 Physiological ranges

To define data that were considered not physiologically possible, the ranges mentioned in Table 8 were used. These ranges are based on a study that described the ABP and HR distributions of critically ill neonates. [84]. For ABP data, margins of 10 to 20 mmHg were used below the 3th percentile and above the 97th percentile of those ABP distributions. No lower limit was defined for the PP data because the mechanism behind the artefacts that cause low PP is relatively complex, an issue which will be addressed in Section A.4.

The 5th percentile and the 95th percentile of the reported HR distributions were approximately 105 bpm and 170 bpm, respectively. However, when visually inspecting the data, it was seen that HR was often in the range of 170-180 bpm and occasionally even higher. Therefore, a wider margin of 80 bpm to 250 bpm was used. For SpO_2, a lower limit of 50% was used. An upper limit was not defined, as it is technically not possible to have SpO_2 values greater than 100%.

Parameter	**Physiologic range**		**Abrupt change**
	Lower limit	Upper limit	Absolute difference
HR	80 bpm	250 bpm	30 bpm $\cdot$ s^{-1}
SpO_2	50%	-	10% $\cdot$ s^{-1}
SAP	30 mmHg	110 mmHg	20 mmHg $\cdot$ s^{-1}
MAP	15 mmHg	80 mmHg	20 mmHg $\cdot$ s^{-1}
DAP	10 mmHg	70 mmHg	20 mmHg $\cdot$ s^{-1}
PP	-	100 mmHg	-

Table 8: Criteria used for detection of non-physiologic values and abrupt changes. Data points outside the physiologic ranges and data points of which the absolute difference with the preceding point were above the limit for abrupt change were considered artefacts and removed. HR = heart rate; SpO_2 = peripheral oxygen saturation; SAP = systolic arterial pressure; MAP = mean arterial pressure; DAP = diastolic arterial pressure; PP = pulse pressure.

A.3 Abrupt changes

Abrupt changes within the vital parameter data which were considered too great to be physiological were also removed. In order to do this, the absolute difference between each sample and the preceding sample was calculated. With a sample frequency of 1 Hz for the vital parameter data, this was equal to the change in one second. Data points with an absolute difference greater than the limits presented in Table 8 were considered artefacts. The absolute difference limits for the ABP values were equal to the criteria of a signal abnormality index for ABP waveforms. [95] The limits for HR and SpO_2 were arbitrarily chosen based on trial and error and visual inspection of the data. As with the non-physiological artefacts, a margin of 5 seconds on each side of detected artefacts was also removed.

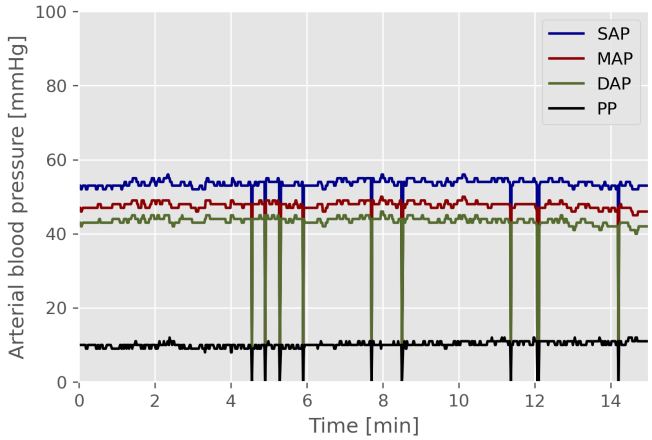

Figure 7: Recording with several moments of measurement artefacts during which all parameters briefly return to zero. SAP, MAP, DAP = systolic, median and diastolic arterial pressure, respectively; PP = pulse pressure.

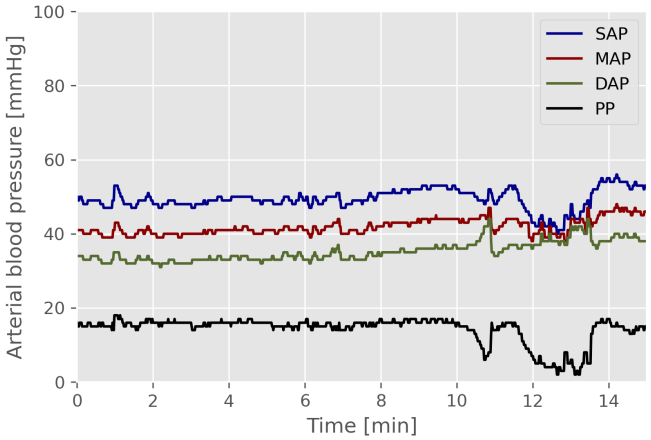

Figure 8: Recording with a period of overdamping lasting for around two minutes. The systolic arterial pressure (SAP) gradually decreases while the diastolic arterial blood pressure (DAP) gradually increases, causing a reduction in pulse pressure (PP). MAP = median arterial pressure.

A.4 Resonance and damping artefacts

Important sources of artefacts are resonance, underdamping and overdamping. Resonance occurs when the frequency of the physiological signal measured matches the undamped natural frequency of the transducer system, causing an increase in the amplitudes of the signal. When a system is not optimally damped, erroneous amplification of the signal occurs when the system is underdamped and erroneous decreases in amplitude will occur in the case of overdamping. Flush tests or square-wave tests can be performed to see whether the system is overdamped or underdamped. [47, 48, 96] Such a test can be seen on the monitor as a square wave, similar to the artefact seen in Figure 2.

Resonance and underdamping can largely be avoided by using catheters and tubing of appropriate length and stiffness, which we assume was the case. Even if resonance and underdamping artefacts occur, it was assumed that with removal of data points outside defined physiological limits (see Table 8), the effects of resonance and underdamping as well as square wave artefacts were detected and removed from the data. While the risk of overdamping can be reduced by using an appropriate measuring system, it can also be caused by air bubbles, blood cloths, or catheter kinks in the system and is therefore a common artefact in clinical practice. [47] Characteristics of artefacts due to overdamping are an overestimation of DAP and an underestimation of SAP, resulting in a decrease in PP. This effect can increase with time, with the PP gradually decreasing until minimal values are reached. An example of a brief period of overdamping can be seen in Figure 8. In order to detect these periods of overdamping, a modified version of the algorithm of Cao et al. [49] was used. The algorithm used consisted of the following steps:

1. smoothing of the PP data using a low-pass second-order forward-backward (zero-phase) Butterworth filter with a cut-off frequency of $\frac{1}{15}$ Hz;
2. selecting series of at least 8 consecutive data points with values below 5 mmHg as potential over-damping sites;
3. scanning the potential overdamping sites forward and backward in time until a point greater than the 25^{th} percentile of the filtered PP data was reached. These points were considered the beginning and end of the over-damping artefact;
4. adding a margin of 5 seconds of data to the beginning of the over-damping artefact to account for disturbances before the artefact and to the end of the over-damping artefact to account for a potential flush test artefact and its consecutive pressure oscillations.

A.5 ECG recordings

The ECG quality assessment method described by Zhao and Zhang [50] calculates four different signal quality indices (SQI) based on the matching degree of R-peak detection (qSQI), the power spectrum distribution of QRS waves (pSQI), kurtosis (kSQI; a measure of signal symmetry) and the relative power in the baseline (basSQI). The different SQI are then fused using simple heuristics to classify the ECG signal as either unacceptable, barely acceptable or excellent. For unknown reasons, the qSQI was not used in the *NeuroKit2* package used in this study. [52] The Pan-Tompkins algorithm used after the quality assessment first pre-processed the ECG signal and then applied several decision rules to detect R-peaks. [51]

When calculating parameters in the frequency domain, which was the case for all HRV measures except SNN, the minimal sample frequency or Nyquist frequency should be at least twice the highest frequency of interest (see Equation 3) in order to ensure adequate sampling of the data. Since the highest frequency to be analysed was 0.4 Hz (the upper limit of HF), the Nyquist frequency is 0.8 Hz. This meant that HR, which was equal to the sample frequency in our data, had to be at least 48 bpm and preferably higher to avoid aliasing. As neonates and infants usually have HR greater than 100 bpm, this was not a problem. [84, 97]

$$F_{nyquist} = 2 \cdot F_{max} \tag{3}$$

A.6 Oximetry measurements

Furthermore, the accuracy of the oximetry measurement device used on our PICU (Masimo SET; Masimo Corporation, Irving, CA, USA) was 1.5% for SpO_2 values between 70% and 100%. [98] With subtracting the postductal from the preductal SpO_2 measurement, the possible measurement error of $dSpO_2$ becomes twice the accuracy of the oximetry. To be safe, the assumed accuracy of the oximetry measurements was rounded up to 2%, resulting in an assumed possible error of 4% for $dSpO_2$ values. Accordingly, all $dSpO_2$ values $\leq$4% were replaced by zero. Moreover, unreliable oximetry measurements can also occur due to sensor disturbances or insufficient contact between the sensor and the skin (e.g. during movement). This can lead to highly variable PLS values, an example of which can be seen in Figure 9. To detect and remove such artefacts, the variance of the PLS was calculated. If the variance of the PLS values was more than three time the variance of the HR values, the PLS and all SpO_2 measurements were considered unreliable and completely removed.

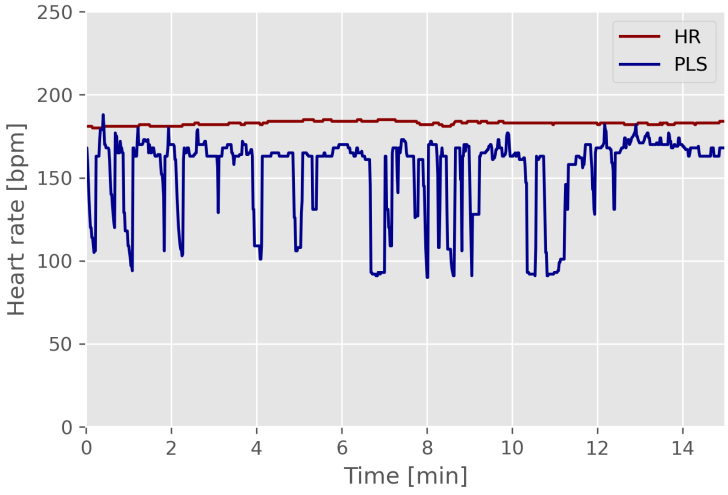

Figure 9: Recording during which the heart rate measurement using pulse oximetry (PLS) shows an erroneously high variability compared to heart rate measurement using electrocardiography electrodes (HR).

B | Cleveland dot plots

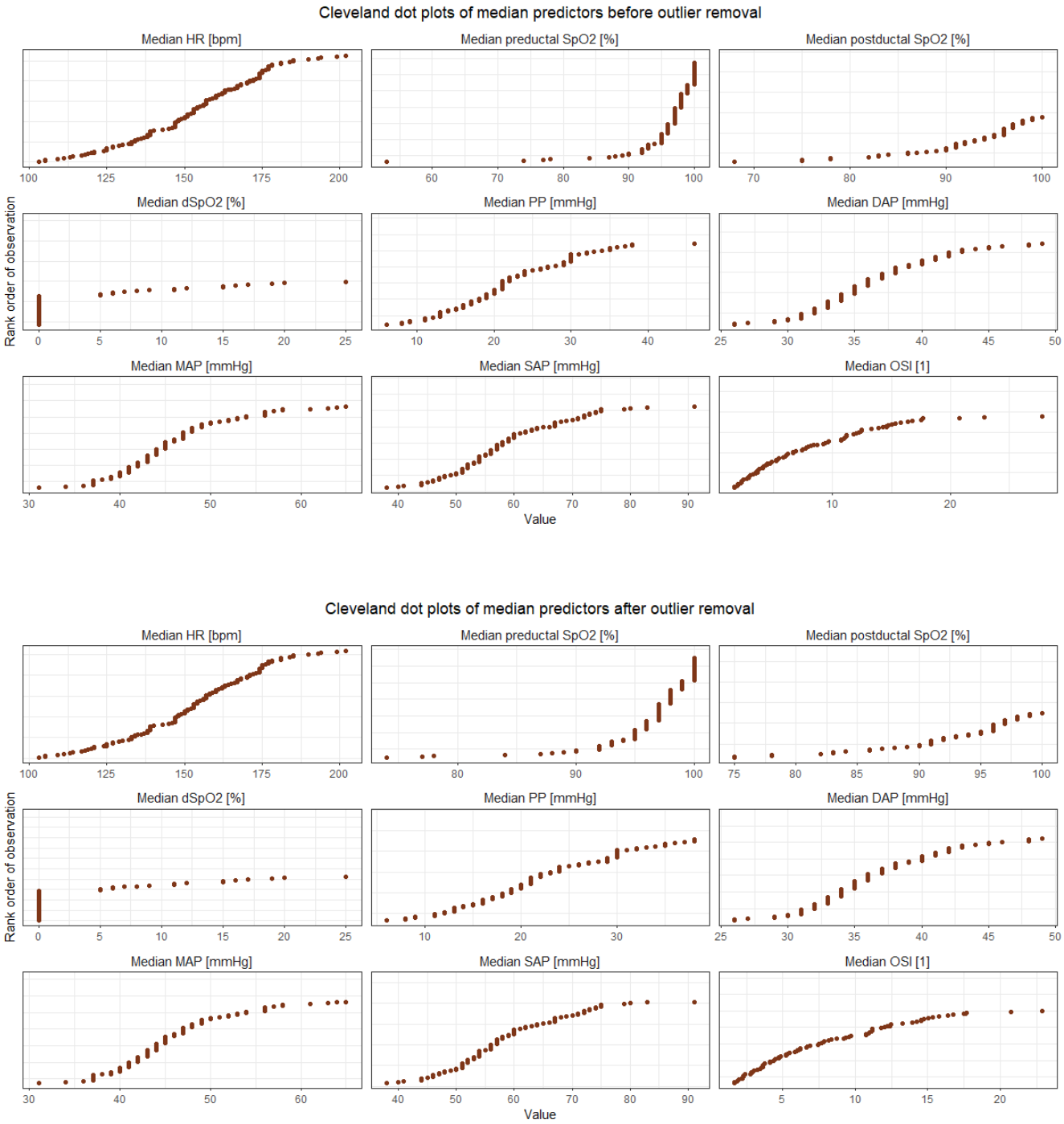

Figure 10: Cleveland dot plots of median predictors before and after outlier removal. HR = heart rate; SpO_2 = peripheral oxygen saturation; $dSpO_2$ = difference between preductal and postductal SpO_2; PP = pulse pressure; DAP, MAP and SAP = diastolic, mean and systolic arterial pressure, respectively; OSI = oxygen saturation index.

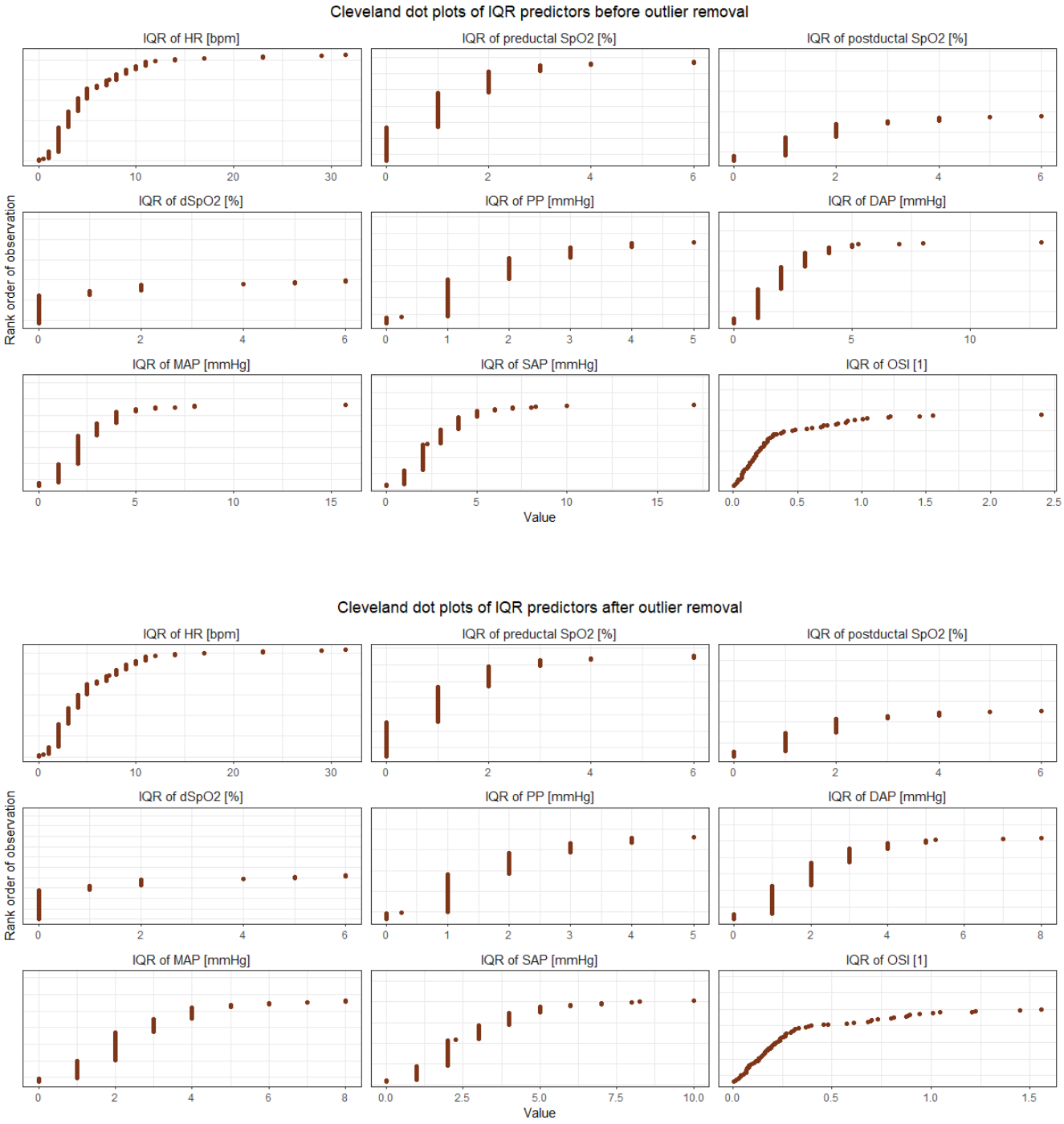

Figure 11: Cleveland dot plots of interquartile range (IQR) predictors before and after outlier removal. HR = heart rate; SpO_2 = peripheral oxygen saturation; $dSpO_2$ = difference between preductal and postductal SpO_2; PP = pulse pressure; DAP, MAP and SAP = diastolic, mean and systolic arterial pressure, respectively; OSI = oxygen saturation index.

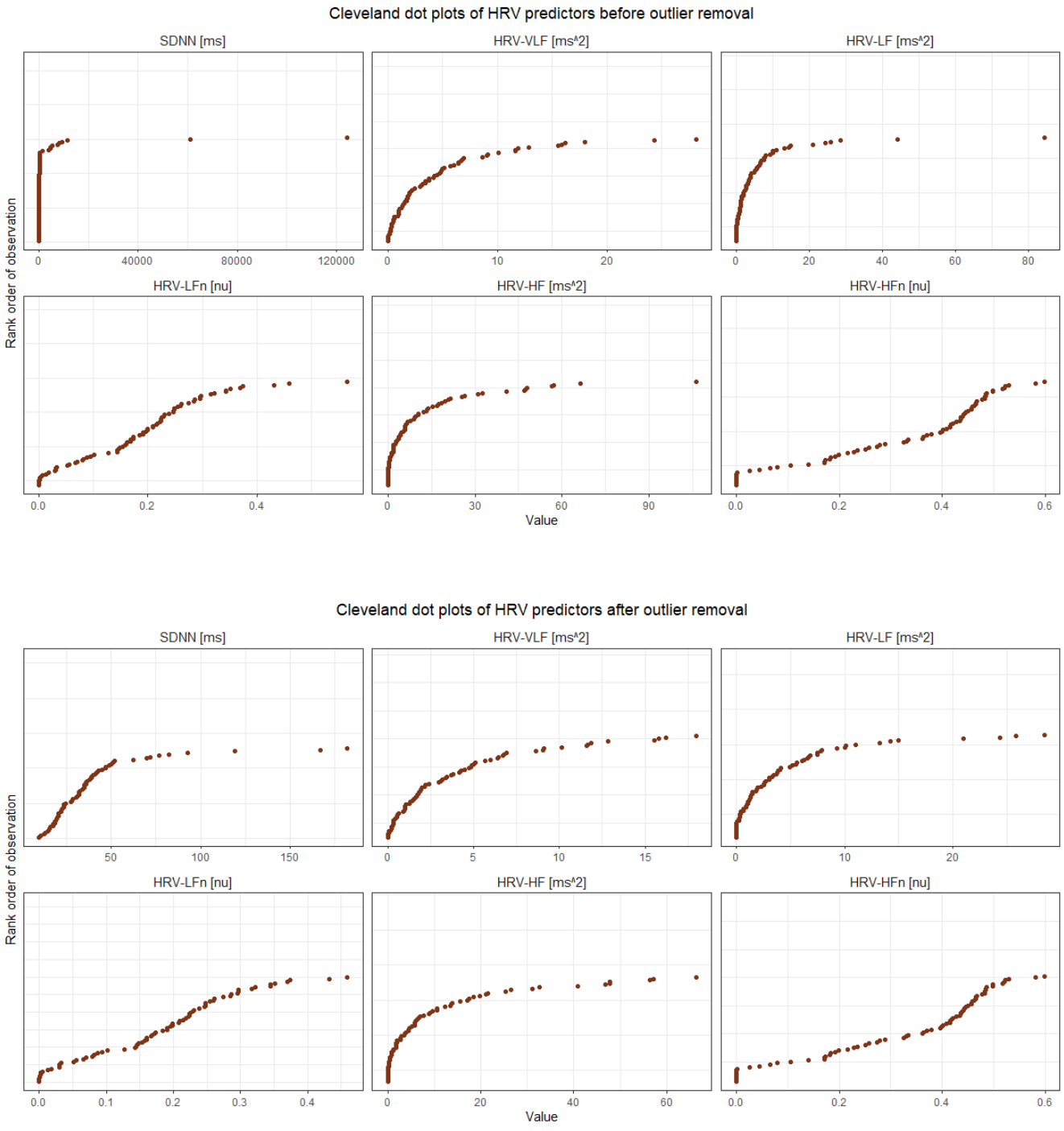

Figure 12: Cleveland dot plots of heart rate variability (HRV) predictors before and after outlier removal. SDNN = standard deviation of the normal-to-normal beat intervals; HRV-VLF, HRV-LF and HRV-HF = total spectral power of heart rate variability in the very low, low and high frequency bands, respectively; HRV-LFn and HRV-HFn = HRV-LF and HRV-HF normalised to the total power, respectively.

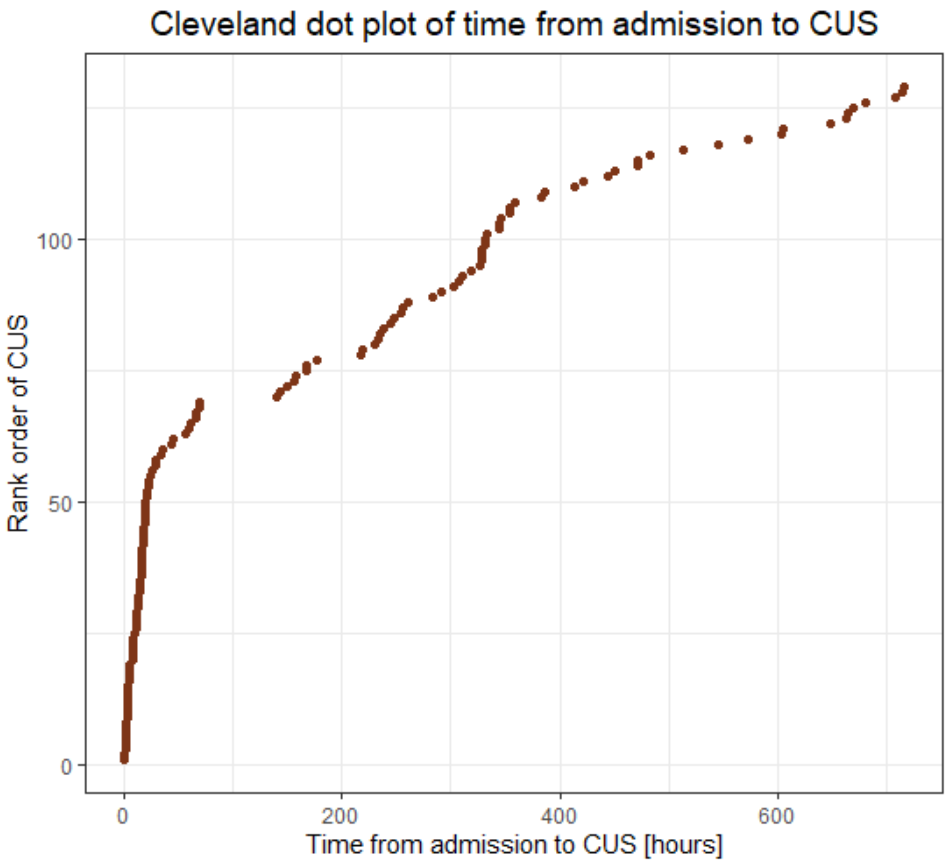

Figure 13: Cleveland dot plot of the time from admission to the moment of cardiac ultrasound (CUS).

C | Boxplots

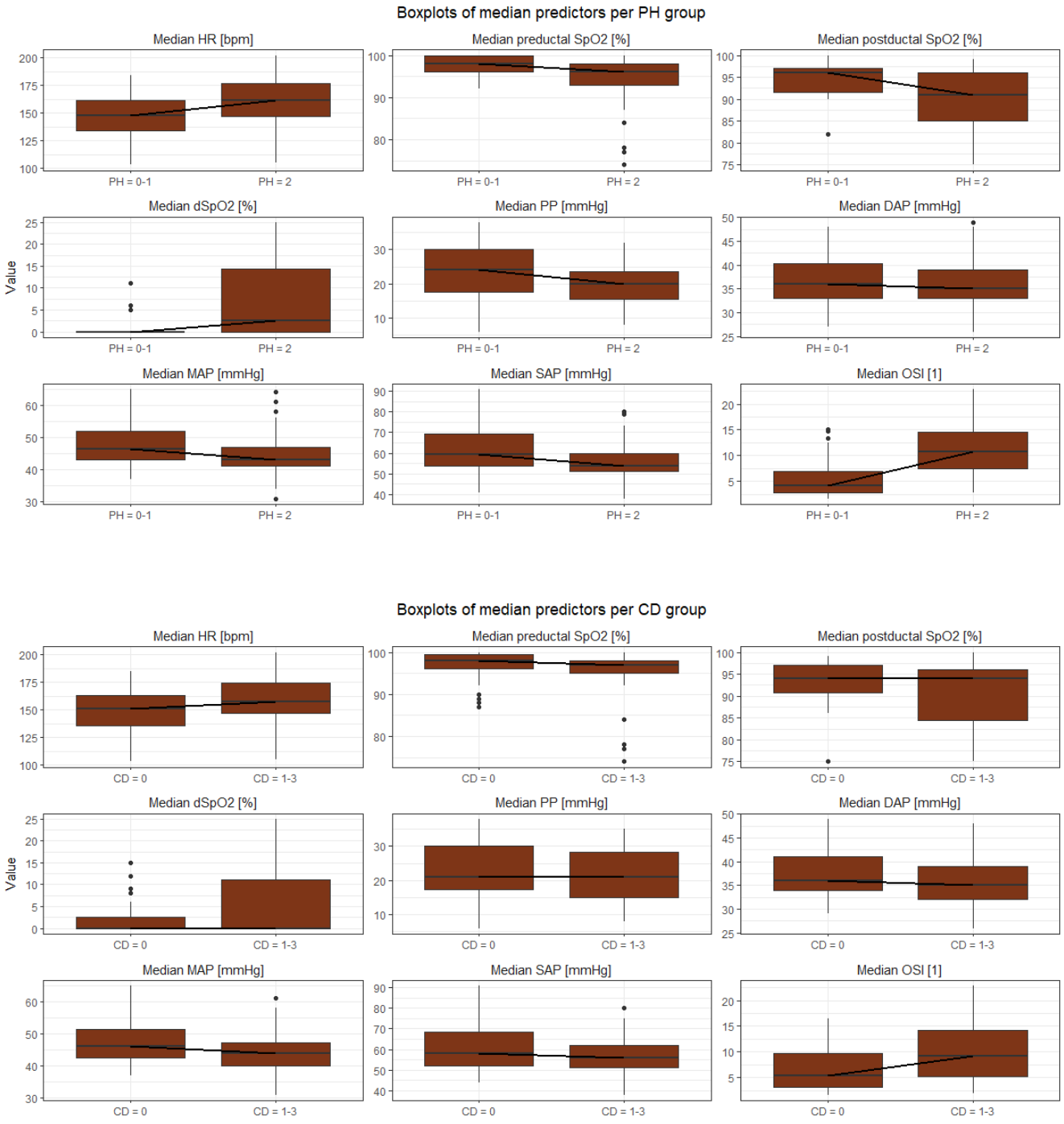

Figure 14: Boxplot of median predictors per group of pulmonary hypertension (PH) and cardiac dysfunction (CD). HR = heart rate; SpO_2 = peripheral oxygen saturation; $dSpO_2$ = difference between preductal and postductal SpO_2; PP = pulse pressure; DAP, MAP and SAP = diastolic, mean and systolic arterial pressure, respectively; OSI = oxygen saturation index.

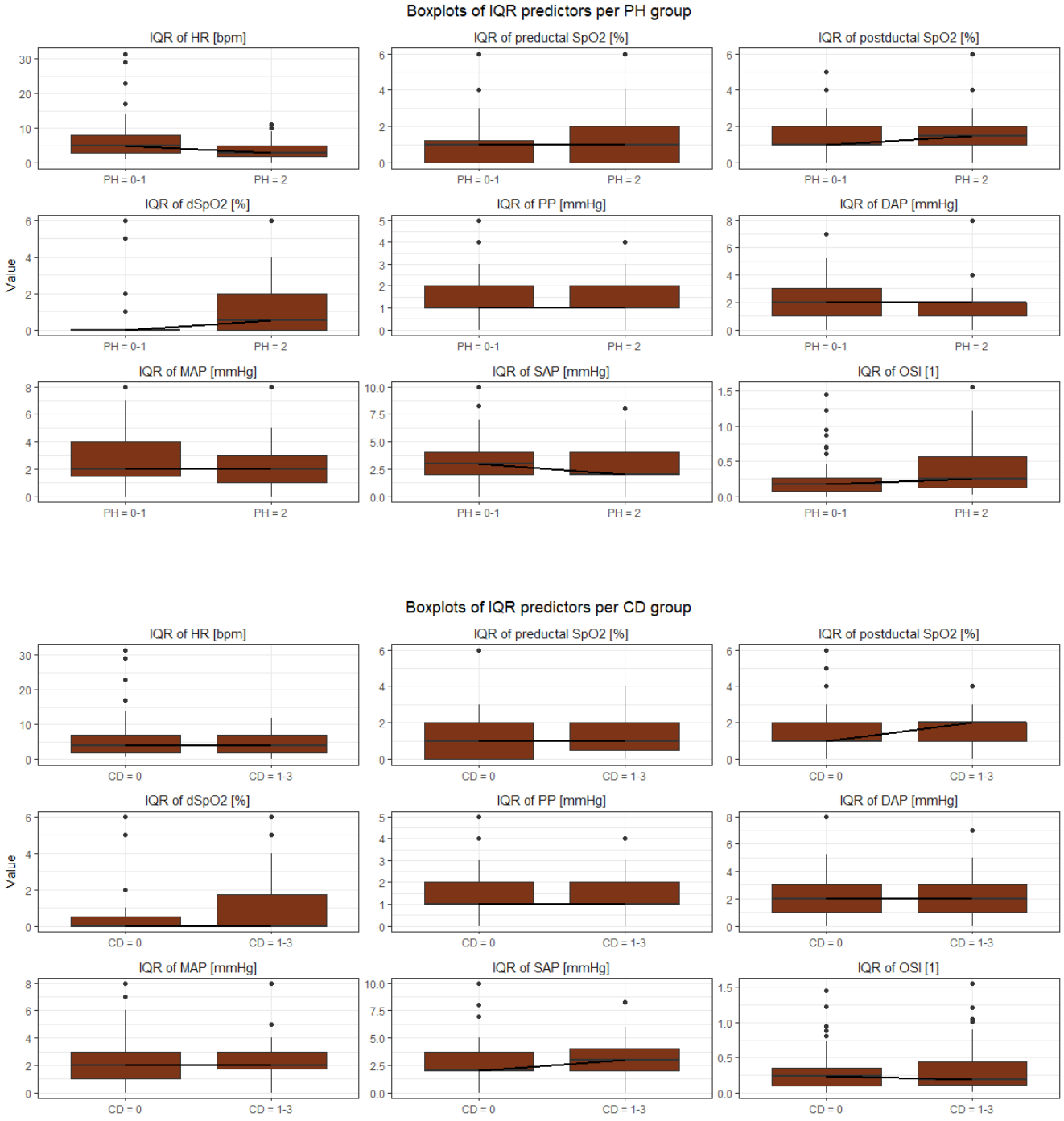

Figure 15: Boxplot of interquartile range (IQR) predictors per group of pulmonary hypertension (PH) and cardiac dysfunction (CD). HR = heart rate; SpO_2 = peripheral oxygen saturation; $dSpO_2$ = difference between preductal and postductal SpO_2; PP = pulse pressure; DAP, MAP and SAP = diastolic, mean and systolic arterial pressure, respectively; OSI = oxygen saturation index.

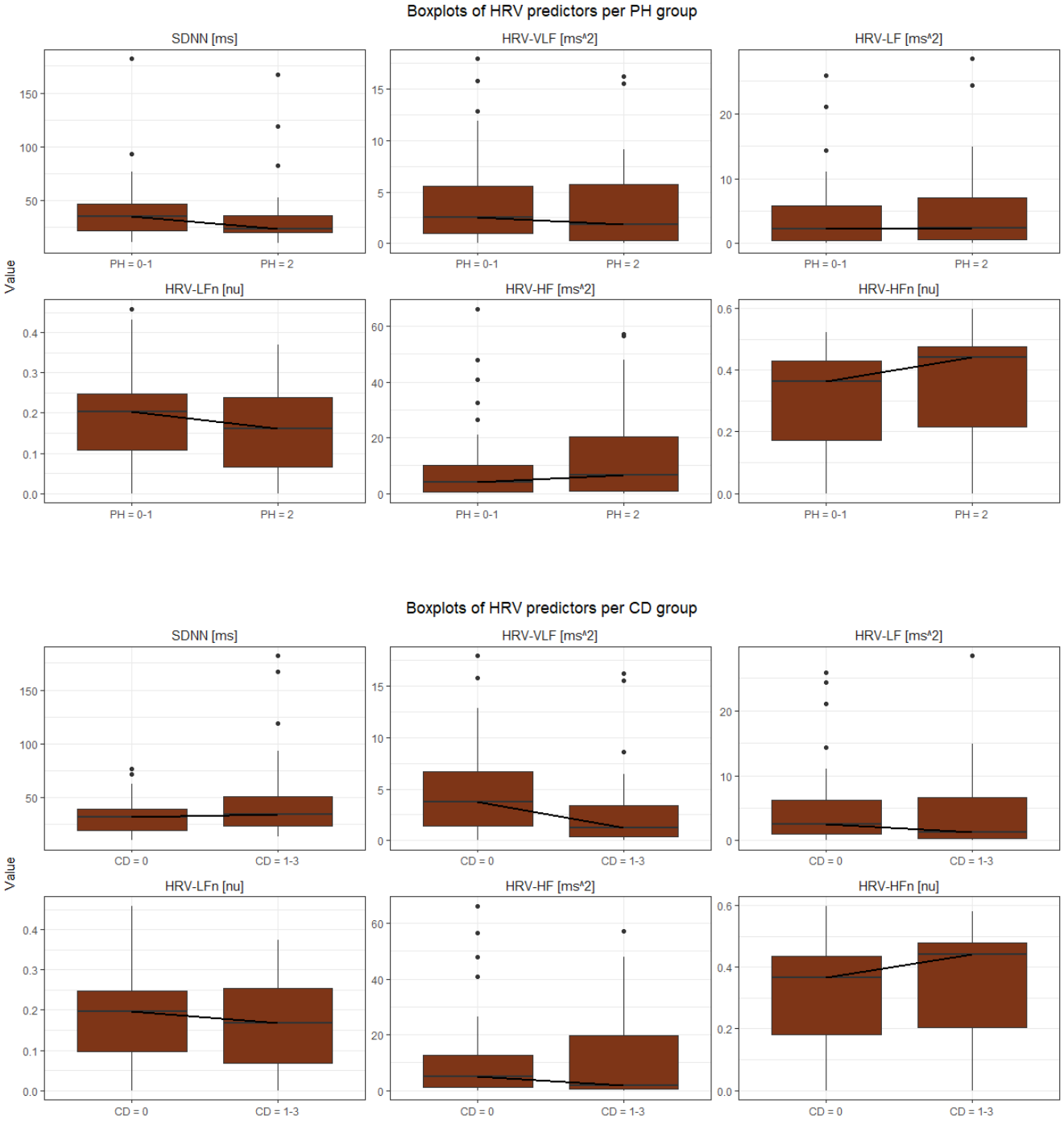

Figure 16: Boxplot of heart rate variability predictors per group of pulmonary hypertension (PH) and cardiac dysfunction (CD). SDNN = standard deviation of the normal-to-normal beat intervals; HRV-VLF, HRV-LF and HRV-HF = total spectral power of heart rate variability in the very low, low and high frequency bands, respectively; HRV-LFn and HRV-HFn = HRV-LF and HRV-HF normalised to the total power, respectively.

D | Quantile-quantile plots

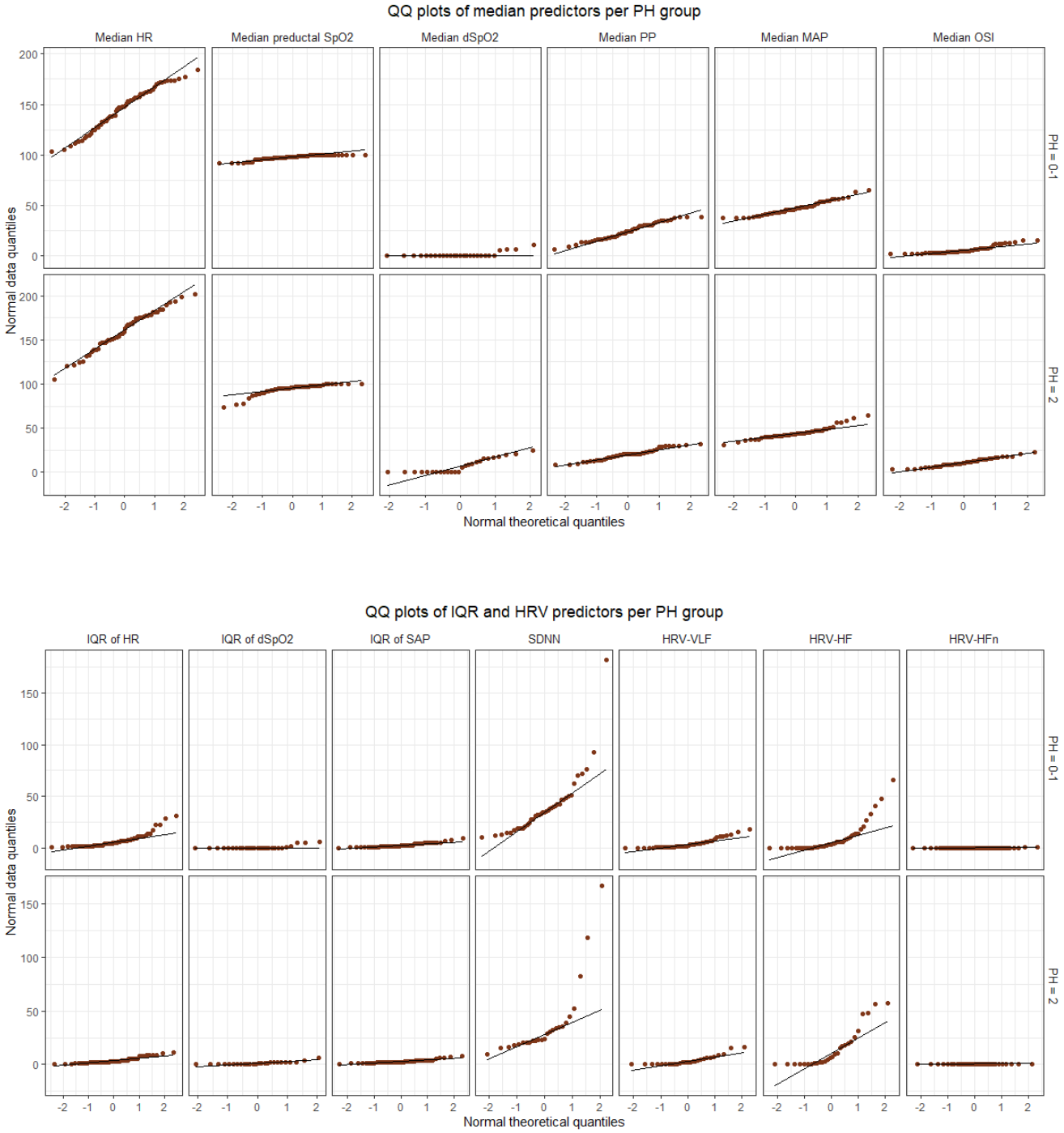

Figure 17: QQ-plots per group of pulmonary hypertension (PH) of all predictors after variable selection. HR = heart rate; SpO_2 = peripheral oxygen saturation; $dSpO_2$ = difference between preductal and postductal SpO_2; PP = pulse pressure; MAP = mean arterial pressure; OSI = oxygen saturation index; SDNN = standard deviation of the normal-to-normal beat intervals; HRV-VLF and HRV-HF = total spectral power of heart rate variability in the very low and high frequency bands, respectively; HRV-HFn = HRV-HF normalised to the total power.

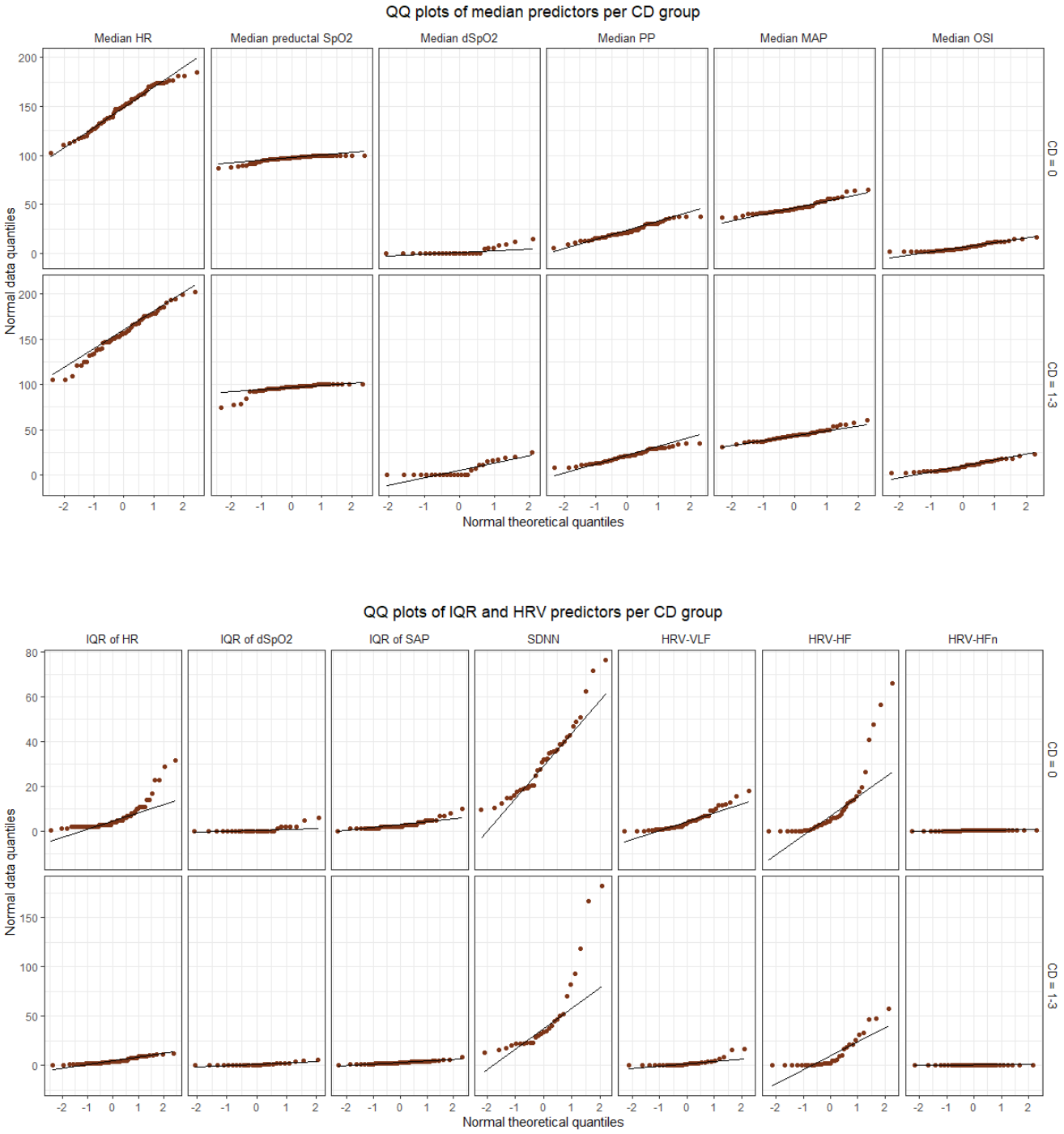

Figure 18: QQ-plots per group of cardiac dysfunction (CD) of all predictors after variable selection. HR = heart rate; SpO_2 = peripheral oxygen saturation; $dSpO_2$ = difference between preductal and postductal SpO_2; PP = pulse pressure; MAP = mean arterial pressure; OSI = oxygen saturation index; SDNN = standard deviation of the normal-to-normal beat intervals; HRV-VLF and HRV-HF = total spectral power of heart rate variability in the very low and high frequency bands, respectively; HRV-HFn = HRV-HF normalised to the total power.