MISSING DATA IN CONTINUOUSLY MONITORED VITAL SIGNS OF HIGH-RISK SURGICAL PATIENTS

MSc Thesis

A.S. Paalvast, BSc
Graduate Intern Technical Medicine
University of Twente
University Medical Centre Utrecht
Division Vital Functions
Department of Anesthesiology

Supervisors

Medical supervisor: dr. T.H. Kappen
Technical supervisor: dr. Y. Wang
Daily supervisor: dr. M.J.M. Breteler
Process supervisors: B.J.C.C. Hessink-Sweep, MSc; drs. R.M. Krol
External member: M.P. Mulder, MSc

UMC Utrecht

UNIVERSITY OF TWENTE.

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Personal information
A.S. Paalvast, BSc (Anne-Lynn)

Educational institution
University of Twente
Drienerlolaan 5, 7522 NB Enschede
Faculty Science and Technology / Techmed Centre
Master Technical Medicine
track: Medical Sensing and Stimulation

Internship
University Medical Centre Utrecht
Heidelberglaan 100, 3584 CX Utrecht
Division Vital Functions
Department of Anaesthesiology
April 2021 - April 2022

Graduation committee

Chair:	Prof. dr. D.W. Donker
	Chair Cardiovascular and Respiratory Physiology, University of Twente
	Intensivist-cardiologist, Intensive Care Centre, University Medical Centre Utrecht
Clinical supervisor:	Dr. T.H. Kappen
	Chief Science Information Officer, Associate Professor, University Medical Centre Utrecht
	Anaesthesiologist, Department of Anaesthesiology, University Medical Centre Utrecht
Technical supervisor:	Dr. Y. Wang
	Assistant Professor, Biomedical Signals and Systems, University of Twente
Daily supervisor:	Dr. M.J.M. Breteler
	Technical Physician, Department of Digital Health, University Medical Centre Utrecht
Process supervisors:	B.J.C.C. Hessink-Sweep, MSc; drs. R.M. Krol
	Teachers 'skillfull communication and professional behaviour', Technical Medicine, University of Twente
External member:	M.P. Mulder, MSc
	PhD candidate, Cardiovascular and Respiratory Physiology, University of Twente

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Abstract

Background

Continuous monitoring of vital signs on a surgical ward could lead to early detection of clinical deterioration, but due to challenges including missing data, wireless monitoring systems are not yet implemented. Little is known on how much data is lost, what causes missing data and how this should be handled.

Methods

24 patients were continuously monitored in an observational study during their stay at the general surgical ward of the UMC Utrecht, after undergoing an esophagectomy or gastrectomy. Heart rate (HR), respiration rate (RR), blood pressure (BP), oxygen saturation (SpO_2), temperature and body position measurements were started when these patients were admitted to the ICU postoperatively. This data was analyzed to quantify the amount of missing data, observations by the research team were screened for causes of missing data and patient cases with adverse events were studied in detail to understand what types of data loss occur in this specific clinical context.

Results

The temperature and body position recordings contained the lowest missing data percentages, followed by heart and respiration rate. Blood pressure and oxygen saturation, measured with a pulse oximeter in an ear clip, had the highest occurrence of data loss, with data loss percentages of up to 100%. Most causes for missing data were related to usability issues and the corresponding missingness of the data was found to be mostly at random (MAR) or not at random (MNAR), outnumbering situations with data missing completely at random (MCAR). Prior to adverse events in four patients, missing data segments that were most likely missing not at random were found.

Conclusion

We found that missing data in continuous monitoring is inevitable, and data loss patterns vary greatly between vital signs and patients. The MNAR segments that were identified, indicate that standard missing data methods are not suitable for dealing with these data gaps. Future research should focus on increasing our knowledge of the clinical context in which data goes missing, building imputation models around data that is missing not at random and validating these models in clinical practice to aid implementation of continuous monitoring.

Abbreviations

AE	Adverse event
AUROC	Area under the receiver operating characteristic curve
BP	Blood pressure
bpm	Beats per minute
brpm	Breaths per minute
CCU	Cardiac care unit
ECG	Electrocardiogram
EHR	Electronic health record
EWS	Early warning score
FiO_2	Fraction of inspired oxygen
HR	Heart rate
ICU	Intensive care nit
IQR	Interquartile range
MC	Medium care
MCAR	Missing completely at random
MAR	Missing at random
MNAR	Missing not at random
PPG	Photoplethysmogram
PTT	Pulse transit time
PWTT	Pulse wave transit time
RR	Respiration rate
SpO_2	Saturation of peripheral oxygen
T	Temperature
VATS	Video-assisted thoracic surgery

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1. Introduction

Vital signs of patients at a hospital ward are generally monitored once per 8-hour shift. Especially during night hours, with fewer medical staff present, patient deterioration can go unnoticed between two consecutive measurements. Clinical deterioration can lead to unplanned intensive care unit (ICU) admissions, resulting in longer hospital stay, increased costs, higher morbidity and mortality [1]. Early detection and intervention of a patient's declining health is therefore essential to prevent or reduce the consequences of these adverse outcomes.

To improve detection of high-risk patients, Early Warning Scores (EWS) have been introduced to quantify the risk of deterioration, since it is often preceded by increasing abnormalities in vital functions. Vital signs - like heart rate (HR), respiration rate (RR) and oxygen saturation (SpO2) - are scored, based on the deviation from standard values, and added to produce one overall risk score. Once the EWS rises above a certain predetermined level, a rapid response team is alerted. Several versions of EWS scores have been developed, i.e. to suit certain patient types, but the evidence is not conclusive on whether the implementation of EWS systems improves patient outcomes [2].

One of the limitations of these scores is that they only reflect a patient's health at a certain point in time. The measurement interval is thus of great influence on the ability of EWSs to detect clinical deterioration: events between intermittent measurements are not captured. By studying slopes between intermittent measurements, Churpek et al found that these trajectories of vital parameters significantly improved the accuracy of detection models when compared to only current vital sign values [3]. Still, the area under the Receiver Operating Characteristic curve (AUROC) value for this enhanced detection was 0.78, compared to 0.74 for a model only containing current values, which means that a lot of events remained undetected. Regular intermittent measurements are too low-frequent to capture all deterioration events on time. However, increasing the measurement rate at regular nursing ward may simply not be feasible, because of the imposed workload on nurses. Therefore, other means of measurement are needed that can monitor patients at a higher frequency to prevent clinical deterioration to go unnoticed between vital sign checks.

Using continuous measurements of vital signs, trends can be studied in real-time and can be based on data obtained every few minutes. This might allow for earlier and more accurate detection of clinical deterioration than detection by standard intermittent vital signs measurements [4][5]. Wireless devices have been developed to give patients more freedom while being monitored, as the need to be attached to a bedside monitor has been eliminated. It even allows for remote patient measurements at home. These devices are often shaped like a patch, watch or band, and are worn on the chest, wrist and/or upper arm. The continuously recorded signals are uploaded to a server, often using a relay device. This device needs to have an internet connection and be in the direct vicinity of the wireless device. This allows the patient to move freely without being attached to fixed equipment, while simultaneously providing nurses with valuable information on their health. Recent studies have shown that these systems are capable of detecting abnormalities in vital signs in high-risk surgical patients who develop adverse events in the days following surgery [6][7]. Nearly all devices measure HR and RR, while other parameters such as oxygen saturation (SpO2), skin temperature, blood pressure and activity are rarely recorded [8].

Despite the promising results, many wireless devices are still in the phases of clinical validation and feasibility testing, and no large well-controlled studies have been performed that show significant cost reduction or clinical benefit [9][10][11]. Khanna et al. identified several challenges that need to be tackled before noninvasive continuous monitoring can be implemented in clinical practice. These include validation of sensor systems, integration of all data sources, reducing artefacts and false alarms, and solving technical connection difficulties [12][13]. The latter two problems may result in data loss. Data loss causes an interruption of clinical monitoring continuity and results in missing data for the use of the data in predictive algorithms and scientific evaluation of the devices. Studies report data loss of up to 35% in heart rate measurements and for oxygen saturation recordings, several cases with up to 100% data loss were found [14][5]. Even though these wireless devices can have clear benefits for patients, the patient's increased mobility and the use of wireless connections cause increased data loss, when compared to conventional wired systems. While conventional monitoring devices for vital signs are always connected to power, wireless devices rely on a battery and need a wireless connection to transmit data. Gaps in measurements can also be caused by (partial) detachment of the sensor due to patient discomfort or care, errors in signal analysis or even unknown causes.

Currently, data loss limits the reliability, usability and the evaluation of wireless continuous monitoring systems. The best method would be to improve the technical and functional designs of the device. However, this is not as straightforward as it may sound, especially in circumstances where the patient is ambulatory, e.g. at the nursing ward or at home. A clinically sound approach to handle data loss in clinical practice is thus warranted. This requires a better understanding of the circumstances in which data loss occurs and what its frequency is. In this thesis, we draw from the statistical-epidemiological framework of 'missing data' to study data loss to evaluate whether methods for handling missing data during data analysis are suitable or can be successfully modified to handle data loss in clinical practice.

2. Background

To understand the concept of data loss and the context in which it was studied in this thesis, it is important to understand how current devices enable continuous monitoring of vital signs and what the impact of data loss is on recognition and prediction of a patient's clinical path. In addition, we need to explore how the framework of missing data relates to the different situations in which data loss occurs and how missing data methods work, before we can seek to apply such methods on data loss during continuous monitoring of vital signs.

Continuous Monitoring Devices: the Nightingale project

The measurements that were used to study missing data, originate from the Nightingale project. This project was initiated to tackle the need for better wireless monitoring of vital signs and identification of high-risk patients. Five leading European academic hospitals (including the UMC Utrecht in the Netherlands) have set up the Nightingale project, in which the Checkpoint Cardio sensor shown in Figure 1 Figure 1: The Nightingale sensor, with the ECG module (A), SpO2 and temperature module (B), rechargeable battery (C), ear sensors (D), temperature sensor (E) and relay device (F).was tested on patients. It includes an online dashboard that displays all continuous measurements and allows for studying of past data. Validation of these sensor's measurements is one of the main goals of the Nightingale project, as well as studying the accuracy of the detection of patient deterioration and the usability from a patient's perspective.

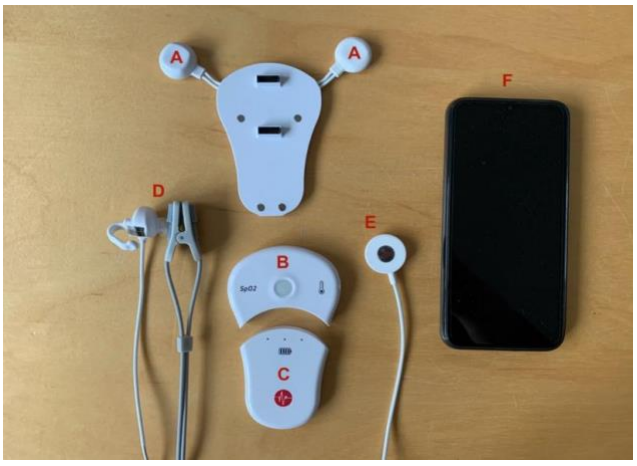

Figure 1: The Nightingale sensor, with the ECG module (A), SpO2 and temperature module (B), rechargeable battery (C), ear sensors (D), temperature sensor (E) and relay device (F).

In this study, patients undergoing esophageal resection were measured from their post-OR admission to the ICU, during their entire hospital stay and often 5 days after discharge at home. These measurements include HR, RR, systolic and diastolic BP, SpO2, temperature and activity, as well as a modified version of the Early Warning Score – NEWS – and a deterioration risk, based on a mainly heuristic model to identify high-risk situations.

During their entire recovery at the hospital and several subsequent days at home, many patients develop complications because of their invasive operation. The continuous recordings of all these vital parameters allow for a detailed study of vital sign behavior leading up to an adverse event, like the occurrence of atrial fibrillation or sepsis, or an unplanned ICU admission. By identifying patterns in these recordings, more knowledge on early manifestations of complications can be gained.

Some of the challenges with this sensor include artefacts and missing data. For all parameters, data gaps occur, often due to detachment of the sensor or a flaw in the processing of the measurements. Some of these can be explained by matching them to appointments at the Radiology department (where the sensor is detached during examination) or the daily switching of the battery, while other instances are caused by measurement, analytical or unknown errors. These gaps complicate the detection of patterns, as it might be harder to find similar trends leading up to the same type of event in different patients. The occurrence of data gaps is inherently tied to continuous measurements and rather than excluding this data from analysis, it should be used to develop reliable methods for dealing with incomplete measurements.

Sensor specifications

The Nightingale sensor is comprised of many different sensor modalities, as each of the vital signs require specific sensing techniques. Heart rate is measured by 1-lead ECG between 2 electrodes, placed the height of the 4th intercostal spaces. These locations correspond with V1 and V2 when compared to a regular 12-lead ECG and the resulting signal corresponds to lead I.
For respiratory rate, the transthoracic impedance is used to derive a continuous respiration waveform. This impedance increases during inspiration, both due to the longer conduction path between the electrodes caused by chest expansion, and due to the increase of gas volume compared to fluid volume in the chest, decreasing conductivity. As air is breathed out, the chest cavity shrinks, bringing the electrodes closer together and lowering the relative gas to fluid volume. The changes in impedance and tidal volume correlate well and can therefore be used to calculate breathing rate [15].

Blood pressure measurements require more than just one sensor component, as they are derived from both the pulse plethysmography signal, measured with the ear sensor, and the ECG-signal. From these signals, the pulse wave transit time (PWTT) – or pulse transit time (PTT) – is derived, defined as the time between cardiac contraction and the arrival of the arterial pulse wave at a peripheral site [16]. For calculations, the time between the R-wave of the ECG signal and the onset of the pulse wave at a peripheral location is used. In some sensors, this peripheral site is the finger, but for the Nightingale sensor it is the ear lobe. The PWTT is inversely proportional to blood pressure, as it depends on blood flow and arterial wall characteristics. It increases in case of a decrease in cardiac output and vascular tone and can therefore reflect concomitant changes in blood pressure.

Temperature is measured by a separate module connected to the sensors' body. It contains a thermistor, a semi-conductor made of different ceramic materials that are thermally sensitive resistors. A current will flow through these materials in response to changes in temperature, as this causes variations in resistance. As temperature increases, the resistance of the thermistor decreases [17]. Body position is derived from an accelerometer in the main body of the sensor, which provides an estimation of the patients' activity.

The ECG-electrodes are not only used for recording multiple vitals, but they are also the main attachment of the sensor to the patient. The temperature and ear sensor are also directly connected to the patient, but the ECG-electrodes are the weight-bearing part.

The impact of data loss

As stated in the introduction, wireless monitoring of mobile patients is prone to data loss due to motion artefacts and connectivity issues. Missing measurements make these devices less reliable, as they impact monitoring in both a diagnostic (how is the patient doing at this moment?) and in a prognostic (is my patients' health deteriorating, staying the same or improving?) way. We miss a reference to test our clinical impression of a patient. At any given moment, we want to be able to check whether the measurements we are seeing are what we expect them to be.

Missing data

Before tackling this data loss problem, more context on the framework of missing data is needed. Missing data is defined as a data value that is not stored for a variable that is being studied [18]. Missing data is generally divided into three categories. This classification of missing data based on its 'missingness' was first defined by Rubin [19]. If data is missing completely at random (MCAR), the cause of absent data is not related to the (missing) observations, i.e., a set of lab samples was not processed correctly. This is often a quite strong and unrealistic assumption, but if true it does not introduce bias. Missing at random (MAR) data is related to the observed, but not the unobserved data. If we know what observed data determines subgroups, and if we can assume MCAR within these groups, the data is MAR. The missingness in the data can be predicted by other features in the data and any bias can be corrected for. An example of MAR is a questionnaire in which men are more likely to fill out their weight than women. If data is missing not at random (MNAR), the fact that it is missing is related to unobserved data, which means it is unknown and correcting for bias is very difficult. MNAR data is also called non-ignorable, because the missing data mechanism needs to be modeled when dealing with this type of missing data. All three types of data are expected to occur to some extent within this study and should be handled with different methods [20][21].

It can be difficult to apply these concepts to clinical situations, as these are often very complex, and many factors can influence the causes of data loss. A correct distinction requires full and detailed documentation, often not at hand in current clinical practice. Still, it is necessary to make accurate assumptions about the origin of data loss, as this determines how the missing values should be dealt with.

Handling missing data

The default method for handling missing data in statistical analysis software, like SPSS, is omitting the missing values. This is done by either list- or pairwise deletion. In listwise deletion, also known as complete case analysis, all cases with a missing value in one of the variables is deleted. Under pairwise deletion, or available case analysis, cases with missing data are considered while ignoring the variables with no value. Both methods only produce unbiased results under MCAR assumption and standard errors are either too large or the required sample sizes are unclear. Even if the MCAR assumption is correct, these methods can still result in a significant additional loss of information. Another simple method of handling data loss is by single imputation, where parameters like the mean or median of a certain variable are used to replace all missing values of that variable. Although this method is quick, it underestimates the variance in the data and introduces bias if the data is not missing completely at random [20]. Due to the large scale, heterogeneity and spatio-temporal variability of the data in this study, simple methods will not improve the data quality and could even worsen its reliability through oversimplification [22].

A more suitable method is multiple imputation. This involves creating multiple predictions for each missing value. The analyses of these multiple sets of imputed data consider the uncertainty in the imputations and yield more accurate standard errors. One of the main benefits is that it can handle MAR and MNAR data. It has to be noted that statistical methods alone are not enough to solve the problem of MNAR and that building a suitable imputation model is difficult [23][24][25].

This is not an exhaustive list of data recovery methods; more – often more computation heavy – methods exist.

3. Objectives

The main research question of this thesis focuses on exploring the concept of missing data in continuous monitoring of vital signs of high-risk surgical patients on a hospital ward, as well as applying current knowledge on handling missing data to this specific clinical context.

Main research question

How can we capture the amount and clinical context of missing data in high-risk surgical patients that are continuously monitored of a hospital ward with a wireless multiparameter system, what types of missing data occur in these measurements and what does this imply for how the missing data should be dealt with?

Two sub-questions are explored to answer this main research question. These research questions are stated below, with the corresponding chapter titles.

Q1: Quantification of missing data and capturing clinical context (Chapter 4)

To what extent could we capture and quantify the clinical context of missing data in patients that are continuously monitored on a hospital ward with a wireless multiparameter system?

Q2: Case studies of missingness before adverse events (Chapter 5)

How can missing data be categorized in patients that are continuously monitored on a hospital ward with a wireless multiparameter system?

4. Quantification of missing data and capturing clinical context

Introduction

Missing data is one of the problems that is complicating successful implementation of continuous monitoring on hospital wards. This problem is maintained due to underreporting of data loss; it is hard to find a reference for how much missing data can be expected and how big the missing data problem is. If it is mentioned, it is often to explain why the missing data is ignored in further analysis. Furthermore, causes of missing data are hardly studied, while these play a role in determining what the impact of data loss is on recognition of early signs of clinical deterioration. Causes that are reported, are mostly nonspecific, captured in broad categories as connection failures, errors in data storage and unknown causes [5].

Causes of missing data are highly dependent on the clinical context in which the data loss occurs: what type of patients are monitored, what type of sensor is used, what care protocols are used? We know that data will get lost, as the sensor has to be detached when taking a shower, switching batteries or applying new ECG electrodes. Missing data is inevitable, but too little is known on what to do when measurements fail.

By providing insight into the occurrence of missing data in continuously monitored vital signs and the clinical context in which this data is lost, important information for how this missing data should be handled can be obtained. In this chapter, we aim to answer the following research question:

To what extent could we capture and quantify the clinical context of missing data in patients that are continuously monitored on a hospital ward with a wireless multiparameter system?

Methods

Two methods of data collection and analysis were used in this chapter. One method was focused on the vital sign measurements, while the other was aimed at observations by the investigators that concerned the usability of the Nightingale sensor during patient monitoring. The workflow of both methods is shown in Figure 2.

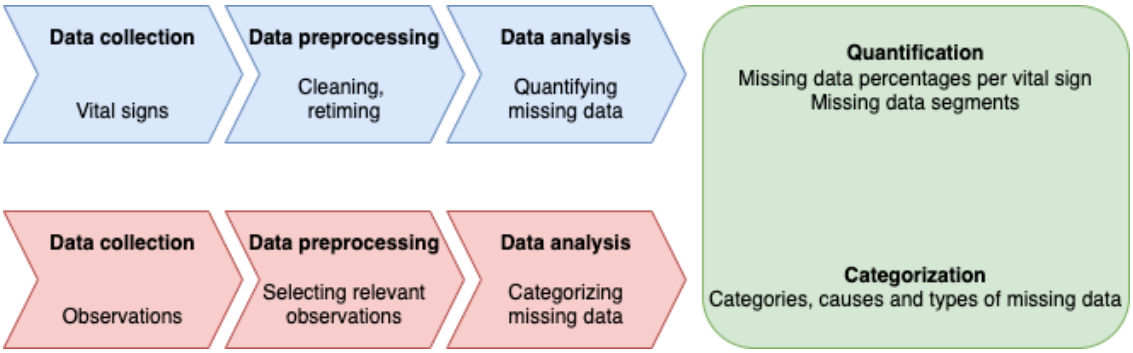

Figure 2: The workflow for the analysis of vital signs and usability observations.

Data collection

For the quantification, the measurements of the Nightingale system for six vital signs were used. The six vital signs are heart rate, respiration rate, blood pressure (systolic and diastolic), oxygen saturation, temperature and body position. The recordings were saved in Excel files with date- and timestamps every 20 seconds, along with average values over this time period for all six measured vital signs.

Throughout the study, daily observations on the usability of the sensor were recorded by the researchers. Any activity or event that was deemed relevant, was recorded in an observation sheet.

Data preprocessing

Only in-hospital recordings were used. Patient discharge dates and times from the electronic health records were used as a cut-off point for vital sign recordings and relevant observations.

All vital sign recordings were exported from the Checkpoint Cardio digital environment and processed in MATLAB (version R2021a, The MathWorks, Inc., Natick, MA, USA). The start times were checked with the case report file (CRF) of each patient. Missing recordings at the start of each measurement were included in the data - these mostly lasted for several minutes due to the calibration of the sensor and relay phone -, but any gaps at the end of each measurement that were recorded after the measurement was stopped (due to a detached sensor where the battery had not yet been removed) were deleted to not falsely increase the percentage of incomplete data. If a recording had been restarted, due to a malfunctioning sensor, all recordings available for this patient were merged.

All values equal to 0 were converted tot 'NaN' (not a number) values, which means they were seen as missing. These could be valid measurements for heart rate and respiratory rate, in case of cardiac arrest or apnea, but none of the patients were resuscitated while wearing the sensor. In case of breathing cessation, this would have to last for longer than 20 seconds to be reflected in the measurements. For some instances of zeroes in heart rate and respiratory rate, the raw data was studied visually. In each case, there was a signal, but due to too much noise, the conversion to a frequency must have failed. Therefore, assuming all zeroes to be missing values might ignore some actual measured values, but the chance that zeroes only occur in case of data loss is much higher.

Any discontinuities in the time arrays were retimed to ensure a regular and complete date and time vector. Due to regular gaps in the time arrays for all measurements, retiming the data sets lead to significant extension in some patients. Through this uniform sampling, missing timestamps were added to the datasets. For missing timestamps that were recovered this way, the value for all corresponding vitals was 'NaN'. After retiming, the 'NaN' values that were already recorded as such were combined with 'NaN' values from recovered timestamps.

The selection of relevant usability observations was carried out by the main researcher. Exclusion criteria for observations were any remarks that did not contain information on the clinical status of the patient or usability of the sensor, or that stated that nothing unusual was seen.

Data analysis

Two different analyses were carried out for the missing data in vital signs. First, data loss as a percentage of the whole in-hospital measurement was calculated for each vital sign in each patient. To study these percentages at a patient level, the spread per vital sign was plotted. This way, the variance within one vital sign for different patients can be studied. Secondly, all missing data segments were extracted.
By looking for all 'NaN' values in the data, consecutive 'NaN' values were combined within the same segment. These segments were visualized in two ways; based on their duration and based on the number of segments that occurred per day of measurement.

All relevant observations were pooled and different missing data categories were defined. For each category, one or more causes for missing data were identified. For each of these causes, the occurrence of situations that could be attributed one of the three types of missing data (MCAR, MAR, MNAR) was studied.

Results

Between December 2020 and September 2021, 25 patients undergoing esophageal resection were included in the study. In one patient, no measurements were conducted as the patient had withdrawn from the study after surgery. Data from 24 patients were analyzed and patient characteristics are shown in Table 1.Table 1: Patient characteristics (n=24)

Table 1: Patient characteristics (n=24)

Gender *n (%)*	Female Male	7 (29) 17 (71)
Age (years) *median [IQR]*		68 [5]
Type of surgery *n (%)*	Esophagectomy Gastrectomy	22 (92) 2 (8)
Length of hospital stay (days) *median [IQR]*		10 [8]
Duration of CPC monitoring (days)	In-hospital, mean (n) At home, mean (n)	8 days (24) 4 days (13)
In-hospital mortality *n (%)*		1 (4)
Readmission within 30 days *n (%)*		2 (8)

Data preprocessing

The duration of measurements that were added to the time array after uniform sampling, had a median of 11:20:00 (hh:mm:ss), with an IQR of 18:28:20. The median percentage of the total duration of the measurement that was added equaled 0.6%, with an IQR of 3.5%.

The largest addition to a measurements' time array had a total duration of 2d 14:07:40 (dd hh:mm:ss), on a complete measurement duration of 3d 18:23:40. This means over two-thirds (68.7%) of the time array was missing in the data before resampling. The smallest addition had a total duration of 2:00:00 (hh:mm:ss), on a complete measurement duration of 5d 14:02:00, accounting for 0.02% of the time array that was initially missing.

Note that the use of the original data, with discontinuous time arrays, would have led to an underestimation of the incomplete data.

Quantifying missing data

The sum of all missing samples per vital sign, per patient, are shown in Figure 3. The variance among different patients is shown in the spread of percentages per vital sign. The lowest percentages of missing data were found in temperature and body position, followed by heart and respiratory rate. Blood pressure and oxygen saturation contained the highest percentages of missing data, with percentages up to 100%.

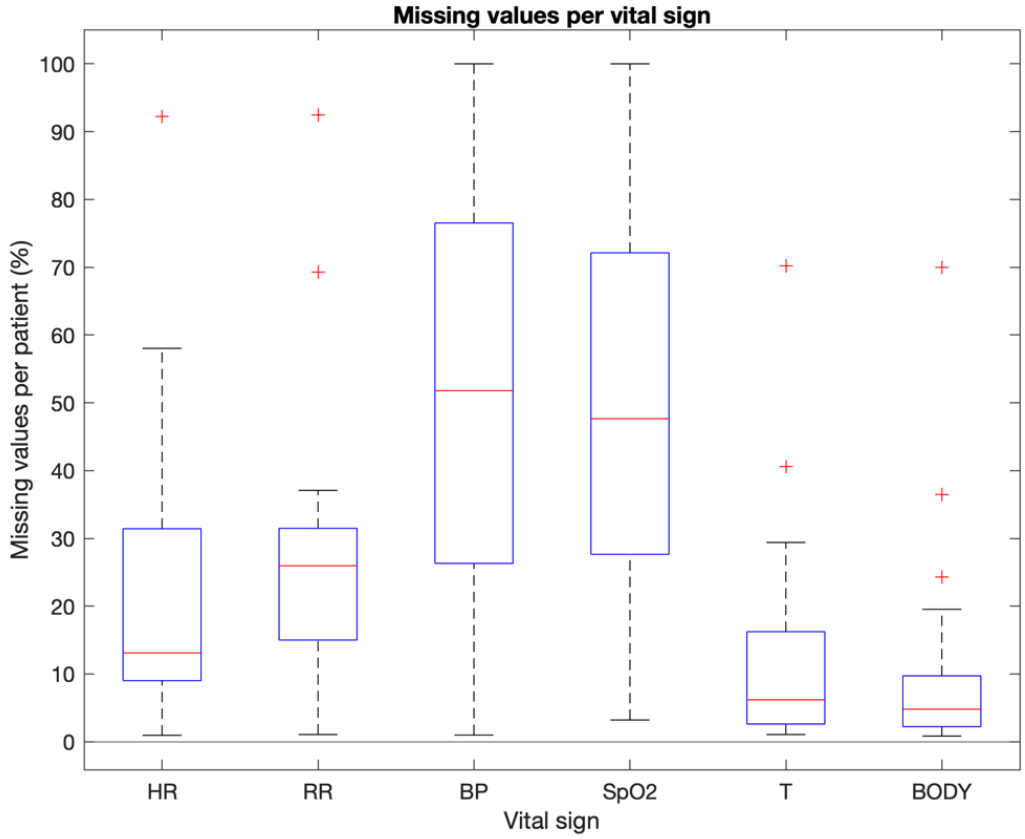

Figure 3: The percentage of missing values per vital sign, plotted as the median (red) and interquartile range (blue) of all 24 patients. HR = heart rate, RR = respiration rate, BP = blood pressure, SpO2 = oxygen saturation, T = temperature, BODY = body position.

The spread of the durations of missing data segments is shown in Figure 4. Blood pressure and oxygen saturation have relatively the longest missing data segments, followed by heart rate. For respiration rate, temperature and body position, missing data segments last relatively the shortest, with over 85% of segments with a duration of less than 5 minutes.

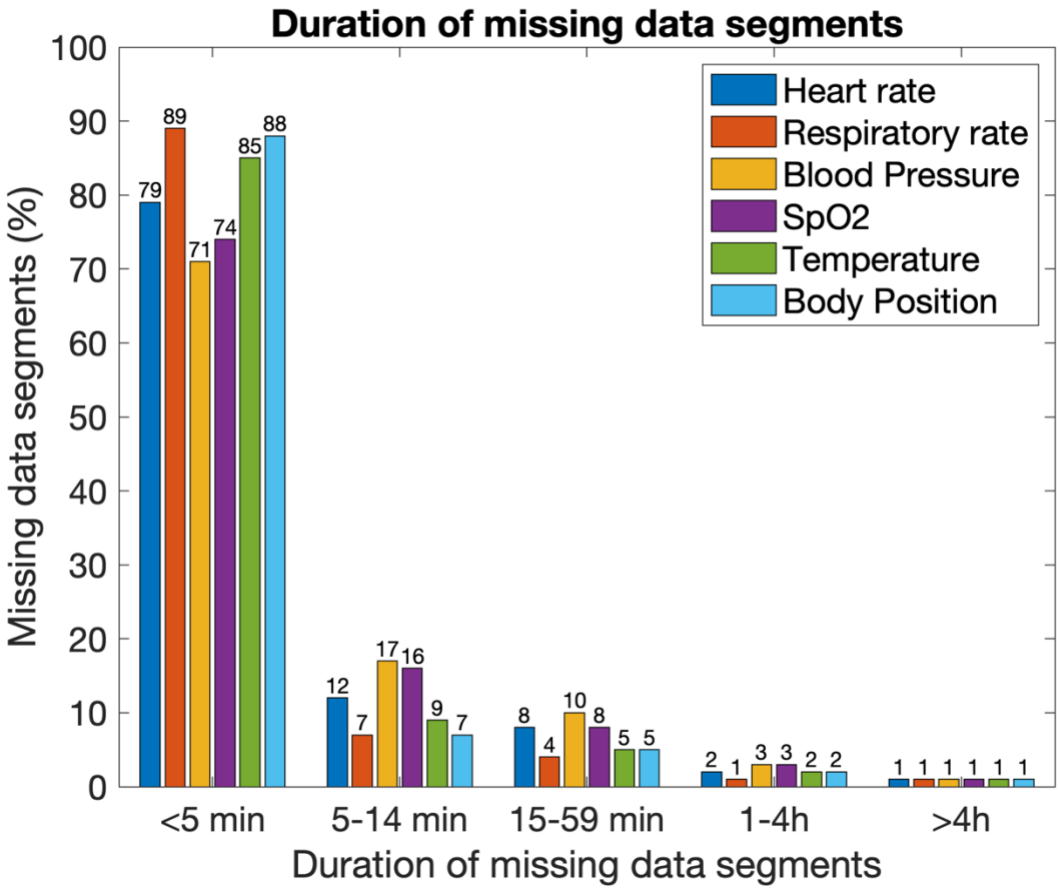

Figure 4: Spread of the durations of missing data segments, as a percentage of the total amount of missing data segments. Displayed percentages are rounded up to the nearest whole number, so these totals can add up to more than 100%.

Figure 5 shows the amount of missing data segments per day of measurement, per vital sign. Segments for different vital signs have overlap and can occur simultaneously. The lowest amount of missing data segments per day occurs in the temperature and body position measurements, followed by heart rate, oxygen saturation and respiration rate. Missing data segments occur most frequently in blood pressure measurements.

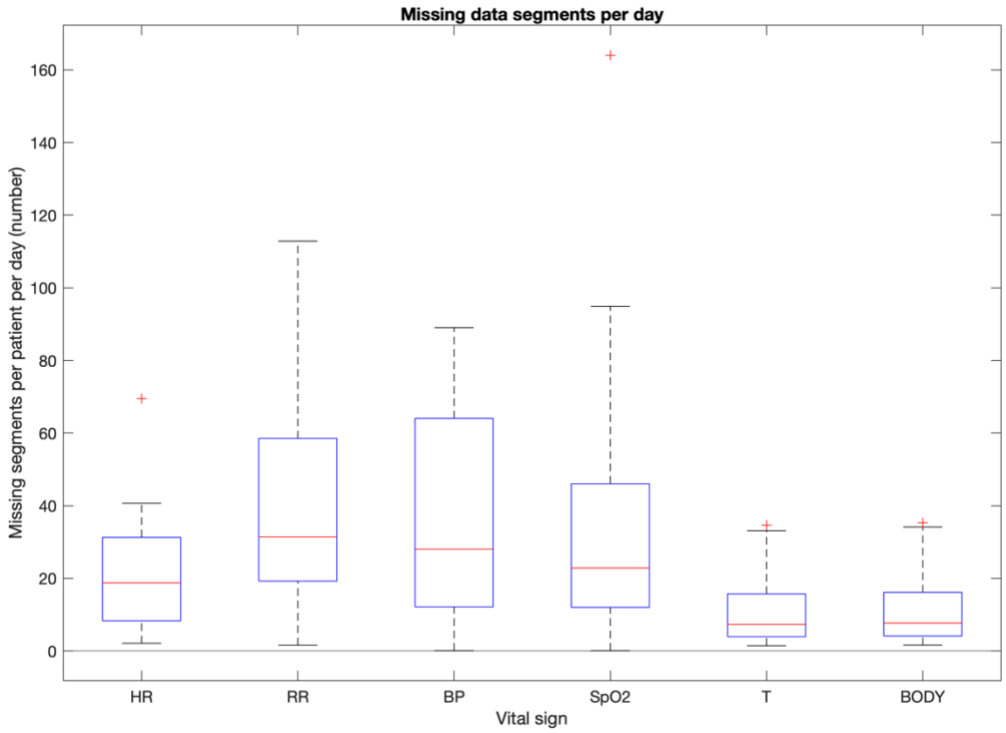

Figure 5: Amount of missing data segments per day, per vital sign, plotted as the median (red) and interquartile range (blue) for all 24 patients. HR = heart rate, RR = respiration rate, BP = blood pressure, SpO2 = oxygen saturation, T = temperature, BODY = body position.

For heart rate, relatively a low total percentage of data is missing, but data gaps last relatively longer when compared to respiration rate. The number of missing heart rate segments per day is quite low. This means that the amount of missing heart rate data is relatively low, but if there is a missing data segment, it lasts relatively long. Respiration rate measurements contain – on average - more missing data than heart rate measurements, but this data loss is divided over shorter and more segments. Temperature and body position measurements have the least amount of missing data, relatively the shortest data gaps and smallest amount of missing data gaps per day. The highest percentages of missing data are found in blood pressure recordings, closely followed by SpO_2 measurements. The relative length of data gaps in these two vital signs are similar, but blood pressure measurements fail more often.

Categorizing missing data

Table 2 shows the different categories of missing data that were identified in all relevant observations, with corresponding causes and types of data loss. For each type of data loss, situations were described to illustrate the differences within one specific cause of missing data.

Table 2: Missing data categories with corresponding causes, types and situations that were encountered in this study.

CATEGORY	CAUSE	TYPE	SITUATION
Usability - **technical**	Empty sensor battery	MCAR	If nurse forgot to change battery while preoccupied with anything else but caring for this patient
		MAR	Too little charging ports available
		MNAR	If nurse forgot to change battery while preoccupied with caring for this patient, due to clinical deterioration
	Empty phone battery	MCAR	Forgot to plug in charger after ward transfer
		MAR	Too little charging ports available
		MNAR	-
	Phone out of range *Bluetooth connection to sensor fails*	MCAR	Phone is left at previous ward
		MAR	Walking around the ward, imaging according to protocol
		MNAR	Extra imaging
	Phone has no connection *Internet connection fails*	MCAR	Provider outage, poor indoor reception
		MAR	-
		MNAR	-
	Processing issues	MCAR	Software errors, crashed phone
		MAR	Motion artefacts
		MNAR	Vitals too high to accurately register, motion artefacts
Usability - **comfort**	Device is detached	MCAR	Accidental faulty reattachment of sensor, piece broken off ear sensor
		MAR	Imaging according to protocol, showering
		MNAR	Sweating, discomfort
	Wrong placement of sensor	MCAR	Poor instructions
		MAR	-
		MNAR	Discomfort
Escalation of care	Device is detached	MNAR	Admission to OR, from ward to MC/ICU, from MC to ICU. Extra imaging.
Unknown	Unknown	MNAR	Unknown

Discussion

Missing data in continuous monitoring is present in each patient, for every vital sign. Our results showed that there is a considerable variance between patients for the same vital sign measurements. Temperature and body position recordings had the least amount of missing data, with median percentages below 10%, as well as the shortest duration and lowest number of data gaps. For heart rate and respiration rate, two vitals that are recorded in the same sensing module, the median percentage of data loss was lower on average in heart rate (26% and 12%, respectively) . Even though missing data segment were less frequent in heart rate, they lasted longer on average when compared to data gaps in respiration rate. Blood pressure and oxygen saturation measurements had the highest percentages of data loss (even up to 100%), relatively the longest data gaps and especially for blood pressure, data gaps occurred very frequently.

An explanation for these differences between vital signs can be found in the sensing method that was used to record them. As blood pressure is the only vital sign that requires two functioning sensor elements (both the PPG signal from the ear sensor and the ECG signal), it is most susceptible to data loss. The ECG signal turned out to be more robust than the PPG signal, but it has to be noted that no correction took place for instances where the ear clip was not worn. Some patients would take off the ear sensor during the night because it hindered their sleep. This means some of the missing data in BP and SpO_2 occurred because the sensor was purposely detached, and not due to software or connectivity issues.

Our study showed that there is a wide range of causes for data loss in continuous monitoring on hospital wards. For most causes, situations with different types of missing data were found. This shows the ambiguity in defining a system to categorize missing data; knowing the cause does not necessarily mean you know the missingness of the data. Although there are cases in which data is most likely MCAR, due to accidental errors or dumb luck, observations describing MAR and MNAR situations far exceeded MCAR situations.
Many different types of discomfort were encountered in the study. From personal preference, to a more worrying ‘every extra wire is too much’, or simply a patient who is done with everyone pulling at his or her body. The exact distinction is often hard to make and matching this situation to the right type of missing data can be difficult.

In the first few patients, an older version of the ear sensor was used, but this in-ear sensor kept falling out and was disliked by most patients. The ear sensor was then upgraded to a clip version, that could be placed on the ear lobe, which led to a higher satisfaction under patients and less missing values. In the first version, a piece of the sensor would sometimes break off, but this problem was not encountered in the ear clip.

Conclusion

Of the six vital signs measured in this study, temperature and body position show the lowest missing data percentages, followed by heart rate and respiration rate. In terms of data loss percentages, duration and number of missing data segments per measurement day, oxygen saturation and especially blood pressure measurements show the highest numbers. For all vital signs, the variance between different patients is quite large.

In a hospital ward setting, causes for data loss can be divided into four categories: usability – technical, usability – comfort, escalation of care and unknown. In this study, situations suggestive of MAR and MNAR exceeded observations that were most likely MCAR.

5. Case studies of missingness before adverse events

Introduction

Understanding the situations in which data loss occurs in-hospital is crucial for substantiating assumptions on the missingness of data, and the most suitable way of handling this missing data. Standard methods, for dealing with missing data, like complete case analysis, assume it is missing (completely) at random, but it is unknown whether these methods are suitable for the application in continuous monitoring in this specific clinical context. Multiple imputation could be an appropriate method, but this does require a thorough understanding of the clinical context to properly substantiate assumptions on the causes of missing data.

Ideally, missing data can be imputed, but this is only possible to perform reliably under the assumption that the data is missing (completely) at random [20][26]. However, MNAR cannot be proven with the available data – since it cannot be verified quantitatively. The issue with missing not at random lies within its very nature; the information that would be needed to prove it, is unobserved. Since MNAR cannot be proven, only assumed, it is difficult to prove that certain missing data occurrences are MNAR. Falsification can be a solution to this challenge. It is a scientific theory developed by Karl Popper, that states that one should attempt to disprove a theory, rather than supporting theoretical hypotheses [27]. In this case, instead of proving MNAR, evidence can be gathered to falsify assumptions of MCAR and MAR, thereby leaving MNAR as the most likely assumption. Therefore, we will identify and describe such situations in detail, to verify any evidence that contradicts premises that are needed to classify missing data as MAR or even MCAR.

As shown in the previous chapter, we see segments of missing values occur simultaneously in all continuous measurements of vital signs. Knowing the technical features of the sensor, this is indicative of connection issues. With the knowledge that no worrying trends precede these gaps, that the EHR states that the patient was walking around the hallway of the ward (without taking the relay device) and with an increase in activity level before and after this missing data, it might seem straightforward to classify this missing data as missing at random. The causes are assumed to be known, and the fact that the patient was walking opposes any notions of clinical deterioration.

Nonetheless, we cannot be sure that this data is missing at random. Due to the sensitivity of the accelerometer in the sensor, it is uncertain whether the increase in activity was only due to walking, or (partly) due to unrest. This is also registered as an increase in movement and as a clinical sign, it would not suggest clinical progress. Would the activity level not have been known, it would have been even harder to support an assumption of missing at random.

Essentially, no studies have been carried out that are aimed at linking types of missing data to data gaps in continuous monitoring on a hospital ward. This underlines the lack of insight into these missingness mechanisms in daily practice and could be an explanation for the persistent missing data problem.

In this chapter, patient cases are studied in detail, to describe the situations where data loss occurred with all context information available within the current setting. We aim to study the following research question:

> *How can missing data be categorized in patients that are continuously monitored on a hospital ward with a wireless multiparameter system?*

Methods

Evidence on the missingness of data gaps was provided by focusing on the measurements directly preceding adverse events that occurred within the Nightingale cohort. The 24 hours leading up to the event were studied to identify the different types of missing data.

Escalation of care was used as a proxy for clinical deterioration, as early clinical signs of adverse events are often poorly defined and deterioration events (like an increase in heart and respiratory rate) are not always well-documented. Five categories were drafted, in ascending order of severity. 'Additional diagnostic testing' was defined as the least severe intervention and included all extra diagnostics, excluding those from routine care. As the next step, 'initiation of treatment' included any extra medication or any surgical or radiological intervention that was required in the next 8-24 hours. If these interventions would not be sufficient and were followed by either a Rapid Response Team consultation, transfer to Medium Care or transfer to CCU/ICU without an emergency intervention, this was categorized as 'escalation of care'. 'Emergency intervention' included resuscitation and/or intubation for a respiratory or cardiac arrest, or an emergency surgical intervention to treat immediate life-threatening conditions. The final intervention category was defined as 'death'.

The list of missing data causes was applied to patient cases where there had been an adverse event. These cases were used to illustrate how missing data in which the missingness is an indicator of clinical deterioration can be identified, i.e. situations where it is expected that important clinical information is lost due to missing data. The adverse events were defined as Medium Care (MC) or intensive care unit (ICU) admissions, and the 24 hours of vital sign measurements prior to this event. The critical missing data segments were highlighted and elaborated on. Missing data segments that were strongly suggestive of clinical deterioration and therefore classified as missing not at random, were emphasized.

Data collection

Data was collected from electronic health records. All reports by the medical team were used to extract relevant information, along with results from radiological imaging and manual vital sign recordings. Continuous measurements from the Nightingale device were used, as well as the observation sheet drafted by the research team.

Data preprocessing

For the definition of an adverse event, an intervention of at least the severity 'escalation of care' was selected. If multiple adverse events had occurred in the same patient, the first was chosen for analysis.
The 24 hours prior to each selected adverse event were studied to define the clinical course of each patient and the amount of missing data per vital sign.
For body position, the 8 different positions were ranked in ascending order of activity: prone, supine, lay left, lay right, sitting, lean back, standing and walking. These positions were given a score from 1 (prone) to 8 (walking). In the data plots, only level 8 refers to physical movement outside the patients' bed.

Data analysis

For each patient case, a brief description of the clinical course and continuous recordings was drafted. For the analysis of vital signs, missing data segments in heart and respiration rate that lasted for more than 5 minutes were selected. Blood pressure and oxygen saturation measurements contained multiple missing data segments with durations up to several hours, which was deemed too long to reconstruct the clinical context in detail. Data gaps in temperature and body position data were only mentioned if these do not coincide with missing data in all other vital signs. For each identified missing data segment, potential causes for missing data were suggested and cases where data is most likely missing not at random (MNAR) were highlighted.

Results

Six patients experienced an adverse event while they were monitored continuously. Two of these events occurred outside of hospital and the remaining four were in-hospital events. The details of these four patient cases, including the clinical outcome and type of adverse event, are shown in Table 3.

Table 3: Overview of the four patient cases on missing data preceding adverse events

Case	***Type of adverse event***	***Days after esophagectomy***
Case 1	MC admission	7
Case 2	IC readmission	6
Case 3	IC readmission from MC	2
Case 4	Emergency surgery (VATS)	9

All four patient cases are discussed in more detail below. Each case contains a similar structure.

- Patient information
  A table containing patient demographics, including age, BMI, type of surgery and type of adverse event.
- Vital sign measurements
  - *Intermittent*
    A table showing vital signs measured periodically by nurses on the ward or Medium Care, comprised of heart rate, respiration rate, blood pressure, blood oxygen saturation, temperature, supplementary oxygen, FiO_2 (in case of supplemental oxygen therapy) and pain score.
  - *Continuous*
    Continuous recordings of the Nightingale sensor in the 24 hours prior to the adverse event are shown. This figure is comprised of six subplots: heart rate, respiratory rate, blood pressure, oxygen saturation, temperature and body position.
- Clinical course
  An overview of the most relevant clinical information in the 24 hours preceding the adverse event, obtained from records and radiology reports in the EHR.
- Continuous measurements
  A concise description of the amount and patterns of missing data in heart and respiration rate.
- Segments
  The duration, time of occurrence and duration of missing data segments in heart and respiration rate that lasted longer than 5 minutes. Additional information is provided on whether all vital signs are missing at that moment.
- Interpretation of missing data
  Overview of the explanations for data loss for a selection of the missing data segments.

Case 1

In Table 4, an overview of patient demographics for this case is shown.

Table 4: Patient demographics of case 1

Age	76
Gender	Male
BMI	32.7
Medical history	Neoadjuvant chemoradiation for cT2N0 distal esophageal adenocarcinoma, 43 packyears, AAA
Surgery type	Open esophagectomy
Type of adverse event	Medium Care admission
Reason for escalation of care	Respiratory insufficiency

In Figure 6, the six vital signs that were measured continuously during the 24 hours preceding the Medium Care admission are shown. All manual intermittent recordings of vital signs were included in this plot.

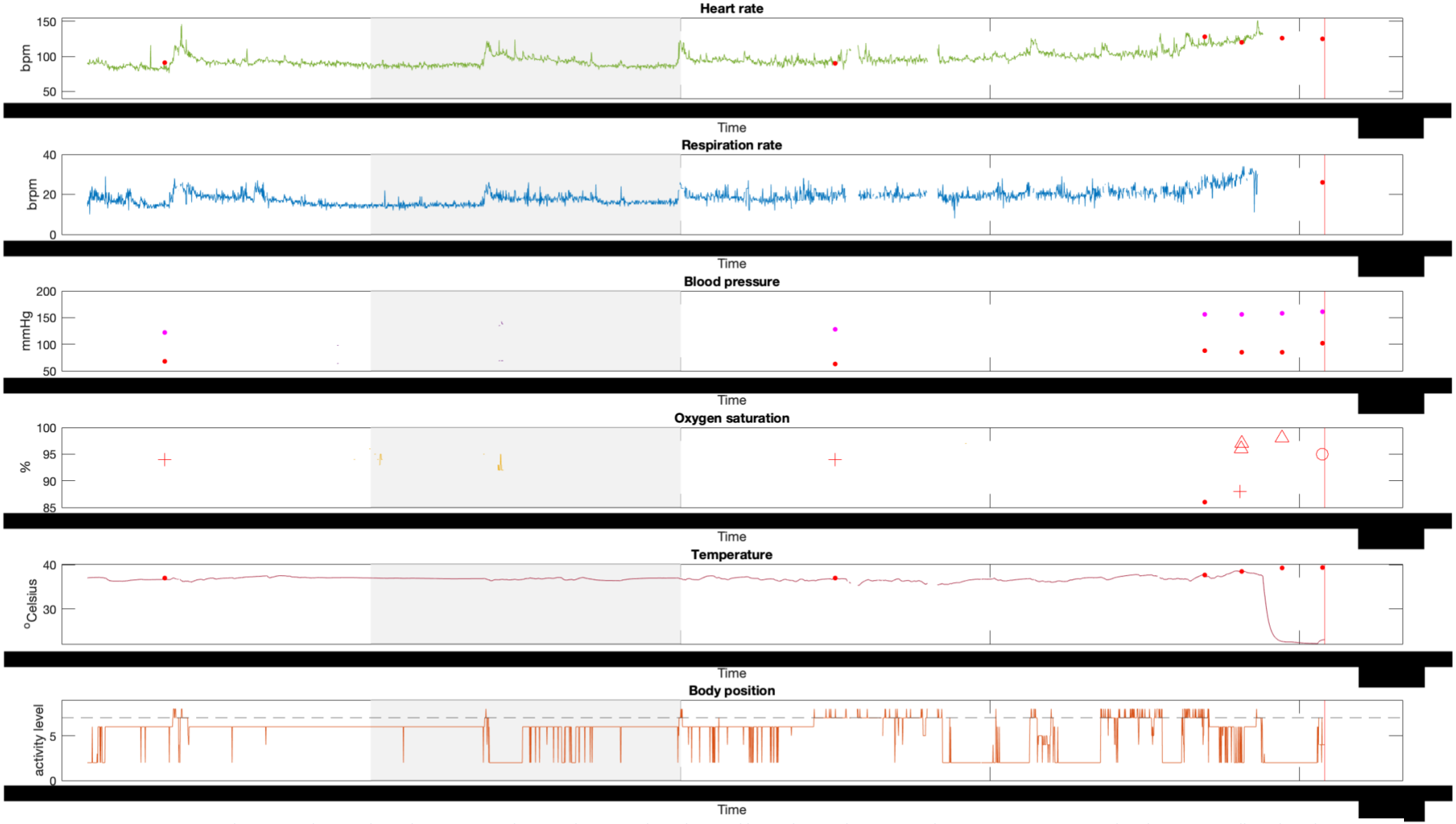

Figure 6: Continuous vital sign recordings in the 24 hours prior to the MC admission. The red vertical line indicates the moment the patient was transported to the MC unit. All marks indicate manual intermittent vital sign measurements, recorded by nurses. Different shapes in oxygen saturation measurements indicate additional oxygen therapy; + = nasal cannula, O = nasal high flow (Optiflow), Δ = Venturi mask.

Clinical course

Six days after the esophagectomy, this patient is hospitalized at the general surgical ward. He has experienced several periods of desaturation (below 90%) for which he received additional oxygen therapy, but does not feel tight-chested. He is successfully following the EROES protocol, and apart from some nights of not sleeping well and some fluid in his lungs seen on chest x-rays, he is recovering steadily.
The night before his MC readmission, the nurse remarked that he sounded like he had an excess of mucus in his lungs and he did not feel like taking his bronchodilating puff medication. He was coughing up slime but, in the morning around 7:00, the ward physician noted that his lung complaints seemed to be decreasing. Shortly after however, around 9:00, the nurse remarked that the patient seemed short of breath and had trouble speaking full sentences. The patient did not agree and indicated he was feeling better. During the day, his oxygen therapy was reduced until he received no additional oxygen. At 15:00, the nurse noted that he had cold shivers and was increasingly short of breath. Oxygen therapy was recommenced after a saturation of 86% was measured shortly before 16:00. This therapy was quickly scaled up to a Venturi mask with 10 liters of oxygen per minute, and heightened further to 15 liters when the response was inadequate. More frequent manual vital sign recordings were performed during the increase of oxygen therapy. Subsequently, the MC physician was consulted and at 18:30, the patient was admitted to the Medium Care due to respiratory insufficiency, requiring Optiflow oxygen therapy,

Continuous measurements

The continuous measurements start with a slightly elevated heart rate and respiratory rate, around 80 beats per minutes and 20 breaths per minute, respectively. Axillary temperature lies around 37 degrees Celsius and the activity level shows a sedentary person. Blood pressure and oxygen saturation measurements are absent. Around 20:00 and 2:30, a spike in heart and respiration rate can be seen, coinciding with an increase in movement. Several oxygen measurements are seen at 2:30, showing levels of around 92%. The rest of the night, a relatively steady heart rate and temperature were recorded, with a more irregular pattern in respiratory rate. At 6:00, another clear increase in heart and respiration rate, and activity level are seen, followed by more irregular patterns in heart and respiration rate, when compared to measurements during the night.
From 12:00, the heart rate shows a rising trend and the same can be seen for respiratory rate from 15:00. The latter is accompanied by an increase in activity, until heart and respiration rate measurements are stopped at 17:15. At this point, temperature and activity levels drop sharply. Some varying activity can be seen right before the MC admission takes place at 18:45.

Missing data

Table 5 shows the total missing percentage for each continuous vital sign, along with the amount of missing data segments and their duration, expressed in median, minimal and maximum values.

Table 5: Total percentages of missing data per vital sign in the 24 hours before the Medium Care admission, the total amount of missing segments and the duration of these segments.

	Total missing (%)	***Missing segments***	***Segment durations (hh:mm:ss, median (min – max))***
Heart rate	6.7	12	00:00:30 (00:00:20 – 00:11:20)
Respiration rate	9.7	47	00:00:20 (00:00:20 – 00:16:40)
Blood pressure	99.6	6	03:06:20 (00:01:00 – 20:46:40)
Oxygen saturation	98.5	8	00:15:40 (00:00:40 – 08:57:00)
Temperature	1.7	11	00:00:20 (00:00:20 – 00:11:20)
Body position	1.6	12	00:00:20 (00:00:20 – 00:11:00)

Blood pressure and oxygen saturation have almost no measurements, while temperature and activity levels only fail in some short instances. Missing data segments in heart rate and respiration rate mostly last less than a minute, with some outliers just above 15 min. Temperature and body position have missing data less than 2% of the time, with most segments lasting for less than a minute and outliers around 11 minutes.

Segments

All missing data segments in the heart and respiratory rate signals with a duration of more than 5 minutes are shown in Table 6. In the continuous measurements of heart rate and respiratory rate, two segments with a duration of more than 5 minutes are seen. The segments of both vital signs happen at the same time and coincide with missing values in all other vital signs.

Table 6: All missing data segments in the continuous heart rate and respiratory rate measurements with a duration of more than 5 minutes, with their time of occurrence and duration, and information on the simultaneous loss of other vital signs. Overlapping segments are highlighted in the same colour.

Vital sign	***Segment***	***Time***	***Segment duration (mm:ss)***	***All vital signs missing***
Heart rate	1	9:18:40	07:40	Yes
	2	10:47:40	11:20	Yes
Respiration rate	3	9:13:40	13:40	Yes
	4	10:47:20	12:20	Yes

Interpretation of missing data

The explanation for these missing segments can be found in the fact that all vital signs are missing during these periods. This only happens when the relay device is out of range or in case of some connection issue. In the electronic health record, it was stated that the physiotherapist had taken this patient for a walk around the ward around 11:00, which would explain segments 2 and 4. Since the patient was able to exercise, this is suggestive of an improvement – or at least not a decrease – in recovery, which would support the hypothesis that this data is missing at random. However, with the current available data, we cannot be sure that this scenario is exactly what happened. The patient might have been very short of breath during the walk, maybe even sat down to rest or walked for a shorter period than intended because he was not feeling well. No continuous blood pressure and oxygen saturation measurements were available, which makes it even harder to interpret the clinical context. The activity level indicates an increase shortly before the data gap, which we assume to be signs of the patient getting ready for a walk, but an increased activity level could also indicate unrest.

Even though it might seem logical that the patient was going for a walk during this data gap, there are too many uncertainties concerning the clinical context, which is why this data is most likely missing not at random.

Case 2

In Table 7 an overview of patient demographics for this case is shown.

Table 7: Patient demographics of case 2

Age	62
Gender	Male
BMI	26.4
Medical history	Hypertension, multiple myeloma, cholecystectomy
Surgery type	Laparoscopic transhiatal esophagectomy
Type of adverse event	Intensive Care admission
Reason for escalation of care	Respiratory insufficiency, suspected aspiration pneumonia

In Figure 7, the six vital signs that were measured continuously during the 24 hours preceding the Intensive Care readmission are shown. All manual intermittent recordings of vital signs were included in this plot.

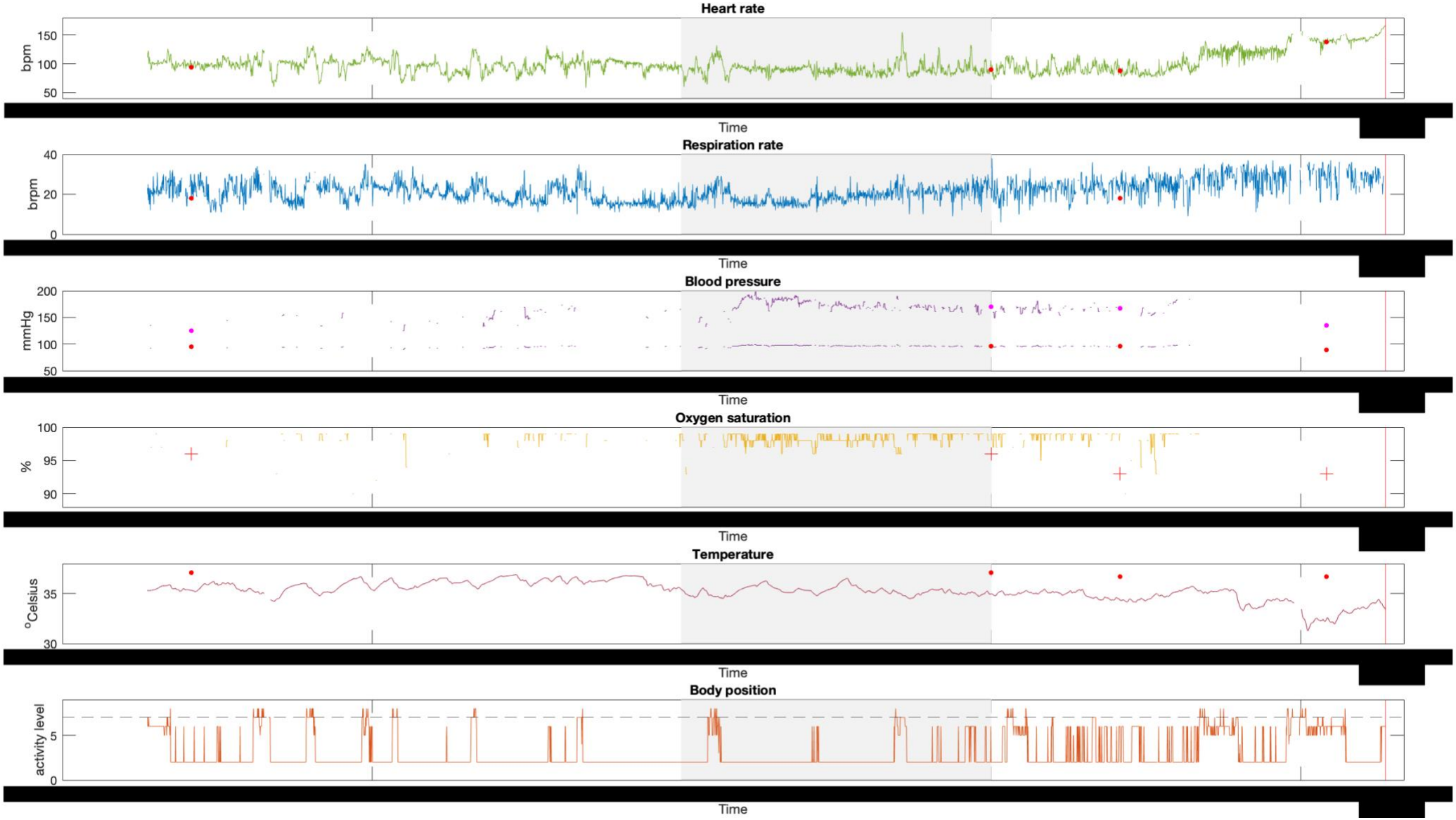

Figure 7: Continuous vital sign recordings in the 24 hours prior to the IC admission. The red vertical line indicates the moment the patient was transported to the ICU from the surgical ward. All marks indicate manual intermittent vital sign measurements, recorded by nurses. Different shapes in oxygen saturation marks indicate additional oxygen therapy; + = nasal cannula.

Clinical course

Five days after the esophagectomy, this patient was hospitalized at the general surgical ward. While he still required oxygen therapy and some increase of pleural fluid and atelectasis was seen on a recent chest x-ray, his postoperative pain was under control, and he was mobilizing daily.
The evening before his admission to the ICU, around 22:00, he was experiencing bowel cramps for which his enteral feeding was lowered. These problems continued during the night and in the morning at 6:00 his condition got worse, as he was feeling nauseous, was painfully coughing up gastric juice, had an excess of mucus in his lungs and was feeling increasingly short of breath at 96% oxygen saturation. He was given primperan at 10:00 to stimulate bowel movement and reduce nausea. This therapy was not adequate, as he kept on coughing up an excess of bile, his oxygen saturation was decreasing to 93% under 4 liters of supplemental oxygen therapy and his respiration rate kept on increasing. His oxygen demand kept rising quickly and he was given a 10-liter non-rebreather mask, which only resulted in a saturation of 92%. He was taken to the ICU at 13:39 due to respiratory insufficiency and a suspected aspiration pneumonia.

Continuous measurements

Heart rate and respiratory rate measurement start at high levels; a tachycardia of 100 beats per minute was measured and a tachypnoea of 20 to 30 breaths per minute. Both vital signs show very irregular patterns until 22:00, when a more stable trend is seen, but at 1:00 at night the irregularity returns, along with a spike in activity. The systolic blood pressure also rises right after this event, approaching 200 mmHg, with a steady but high diastolic pressure of around 90 mmHg. Oxygen saturation varies throughout the night and stays above 95%. From 3:00 respiration starts to rise and this doesn't cease until the ICU admission. Heart rate and activity steeply increase at 10:00, with activity decreasing after an hour, but the rising trend in heart rate continues. This spike at 10:00 is preceded by a saturation drop to 93%, after which this signal is lost, along with blood pressure. Axillary body temperature varies between 35 and 36 degrees Celsius throughout the entire 24-hour period, dropping below 35 degrees at 11:00.

Missing data

Table 8 shows the total missing percentage for each continuous vital sign, along with the amount of missing data segments and their duration, expressed in median, minimal and maximum values.

Table 8: Total percentages of missing data per vital sign in the 24 hours before the Medium Care admission, the total amount of missing segments and the duration of these segments.

	Total missing (%)	Missing segments	Segment durations (hh:mm:ss, median (min – max))
Heart rate	1.7	7	00:01:20 (00:00:20 – 00:08:20)
Respiration rate	5.4	52	00:01:00 (00:00:20 – 00:09:00)
Blood pressure	72.6	202	00:02:40 (00:00:20 – 03:50:20)
Oxygen saturation	61.8	79	00:03:40 (00:00:20 – 01:14:20)
Temperature	1.1	2	00:03:40 (00:00:20 – 00:07:00)
Body position	0.7	2	00:02:30 (00:00:20 – 00:04:40)

Blood pressure and oxygen saturation have measurements less than 50% of the 24 hours, while temperature and activity levels only fail in some short instances. Missing data segments in heart rate and respiration rate mostly last around a minute, with some outliers just below 10 minutes.

Segments

All missing data segments in the heart and respiratory rate signals with a duration of more than 5 minutes are shown in Table 9. In the continuous measurements of heart rate and respiratory rate, three segments with a duration of more than 5 minutes are seen. Two of these segments happen simultaneously and coincide with missing values in all other vital signs. Data in segments 3 and 6 did not go missing at the same time and not all other vital signs were lost.

Table 9: All missing data segments in the continuous heart rate and respiratory rate measurements with a duration of more than 5 minutes, with their time of occurrence and duration, and information on the simultaneous loss of other vital signs. Overlapping segments are highlighted in the same colour.

Vital sign	Segment	Time	Segment duration (mm:ss)	All vital signs missing
Heart rate	1	15:55:00	5:40	Yes
	2	11:51:40	8:20	Yes
	3	12:03:00	5:40	No
Respiration rate	4	15:55:00	5:40	Yes
	5	11:49:40	9:00	Yes
	6	12:46:00	7:40	No

Interpretation of missing data

There are two pairs of missing data segments in the heart rate and respiration rate measurements; 1 and 4, and 2 and 5 occur simultaneously. Both these pairs occur when all other vital signs are missing as well, which is indicative of connectivity problems. For segment 3, the heart rate is the only missing vital sign and the same is valid for respiration rate in segment 6.

Several events that could raise some worry preceded segments 2 and 5. At 11:29, the nurse noted that the patient had a saturation of 93%, as opposed to 96% saturation at 6:00, while additional oxygen therapy was still at 4 liters per minute. The patient was coughing up bile and had a heart rate of 140 beats per minute. His need for oxygen was quickly increasing. Taking this information into account, this missing data segment could have been during clinical deterioration, as it was preceded by clear increasing trends in heart rate and respiration rate.

If the nurses would have been able to see the increasing heart rate and respiratory trends during the night, along with the fluctuations in oxygen saturation under a similar level of oxygen therapy, this could have aided early escalation of care. The missing data segments that occurred within 2 hours prior to the ICU admission were an extra indicator that the patient's health was rapidly declining. In this case, the missingness can be seen as an indicator for clinical deterioration.

Case 3

In Table 10, an overview of patient demographics for this case is shown.

Table 10: Patient demographics of case 3

Age	76
Gender	Male
BMI	26.6
Medical history	Radio- and chemotherapy for cT3M0N0 adenocarcinoma esophagus Extensive cardiac history, including multiple dotter treatments and RF ablation for paroxysmal atrial fibrillation
Surgery type	Robot assisted esophagectomy
Type of adverse event	Intensive Care admission from Medium Care
Reason for escalation of care	Respiratory insufficiency

In Figure 8, the six vital signs that were measured continuously during the 24 hours preceding the Intensive Care readmission are shown. All manual intermittent recordings of vital signs were included in this plot. Since this patient was hospitalized at the Medium Care, the intermittent vital signs were recorded much more frequently than at the surgical ward.

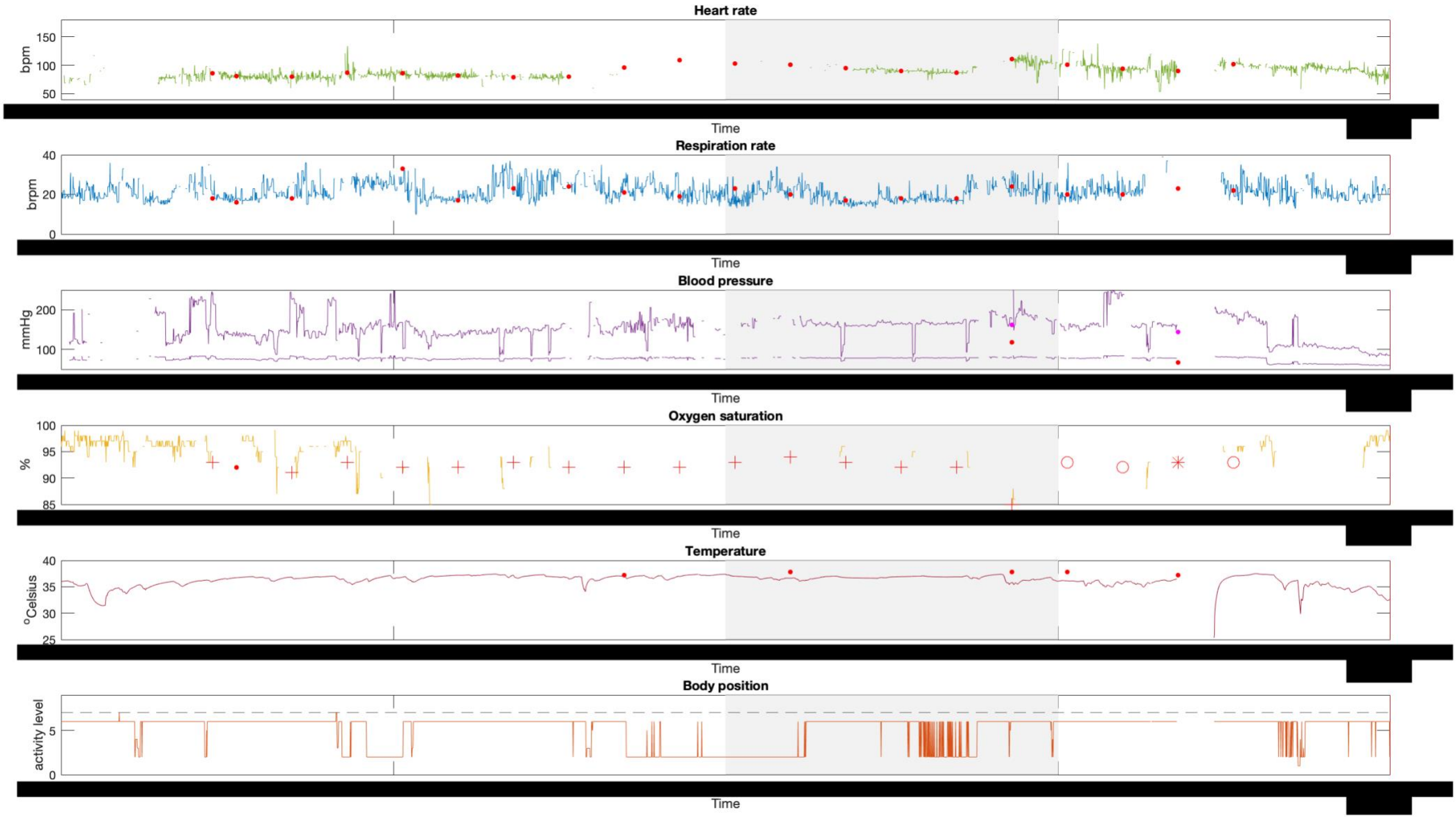

*Figure 8: Continuous vital sign recordings in the 24 hours prior to the ICU admission. The red vertical line indicates the moment the patient was transported from the MC to IC unit. All marks indicate manual intermittent vital sign measurements, recorded by nurses. Different shapes in oxygen saturation marks indicate additional oxygen therapy; + = nasal cannula, O = nasal high flow (Optiflow), * = non-rebreather mask.*

Clinical course

One day after the esophagectomy, this patient is hospitalized at the Medium Care unit, after spending the postoperative night at the post-anesthesia care unit (PACU). His pain is under control with his epidural, no hemodynamic support is needed for a stable blood pressure, oxygen saturation is kept above 92% with 5 liters of oxygen per minute and there is some subcutaneous emphysema in his neck, near the suture. His work of breathing is still quite high and he is quickly exhausted after respiratory exercises, which prevented him from mobilizing on the first morning after his surgery. Even though his recovery could be better, he indicates that – considering the circumstances – he is doing okay. At 14:30, he is transported to the Medium Care. The doctors notice that his neck seems to expand when he is coughing, and on the chest x-ray that is ordered at 16:40, a pneumothorax is seen. A thorax drain is placed and another chest x-ray confirms it is in the right position. In the evening, at 22:30, a sinus tachycardia of 105 beats per minute is seen by the nurse. The patient has not used his antihypertensive and heart medication since the surgery, and it is decided that the tachycardia will be accepted if it stays below 110 beats per minute.
During the night, the patient had increasingly more pain at the site where the thorax drain was placed and was getting short of breath with 90% oxygen saturation with 6 liters of additional oxygen per minute. At 5:30, antibiotics were administered and Optiflow therapy was started. A chest x-ray and CT scan were taken which revealed a persisting pneumothorax and anastomotic leaking. Oxygen saturation was raised slightly to 92%, and the thorax drains were repositioned. An intensivist was consulted and the patient was admitted to the ICU for respiratory insufficiency with severe atelectasis and sputum stasis.

Continuous measurements

The patient's heart rate starts off quite steady at around 80 beats per minutes, 24 hours before the ICU transfer. Respiratory rate is about 20 breaths per minute, with peaks up to 30. Systolic blood pressure is varying between 200 and 120 mmHg, diastolic blood pressure is steady around 80 mmHg. Oxygen saturation varies between 95 and 98%, while axillary temperature is fluctuating around 35 degrees Celsius, accompanied by little activity. Especially heart rate and blood pressure show missing values in the first few hours that follow, while respiratory rate and oxygen saturation keep an irregular pattern. Around 19:00, there are some deep desaturations to 85%, after which the saturation signal fails. Blood pressure and respiration rate keep on fluctuating throughout the night, while the sparse heart rate measurements that are available show a relatively stable rhythm of about 85 beats per minute. An hour-long gap in all measurements can be seen in all vital signs around 8:00, preceded by rising trends in heart and respiration rate. After the signal is recovered, temperature increases rapidly and all other vital signs show similar behavior as before this gap, continuing until the ICU admission.

Missing data

Table 11 shows the total missing percentage for each continuous vital sign, along with the amount of missing data segments and their duration, expressed in median, minimal and maximum values.

Table 11: Total percentages of missing data per vital sign in the 24 hours before the Intensive Care admission, the total amount of missing segments and the duration of these segments.

	Total missing (%)	***Missing segments***	***Segment durations (hh:mm:ss, median (min – max))***
Heart rate	38.3	72	00:02:00 (00:00:20 – 01:28:20)
Respiration rate	10.8	50	00:01:20 (00:00:20 – 00:47:20)
Blood pressure	18.5	89	00:02:20 (00:00:20 – 00:41:00)
Oxygen saturation	77.0	34	00:15:40 (00:00:20 – 02:40:00)
Temperature	2.8	2	00:00:30 (00:00:20 – 00:00:40)
Body position	2.8	2	00:00:30 (00:00:20 – 00:00:40)

Heart rate and oxygen saturation have measurements less than 62% and 23% of the 24 hours, respectively, while temperature and activity levels only fail in some short instances. Missing data segments in blood pressure and respiration rate make up between 10-20% of the time.

Segments

All missing data segments with a duration of more than 5 minutes are shown in Table 12.

Table 12: All missing data segments in the continuous heart rate and respiratory rate measurements with a duration of more than 5 minutes, with their time of occurrence and duration, and information on the simultaneous loss of other vital signs. Overlapping segments are highlighted in the same colour.

Vital sign	Segment	Time	Segment duration (hh:mm:ss)	All vital signs missing
Heart rate	1	12:36:40	5:20	No
	2	12:47:20	57:00	No
	3	14:43:20	6:40	No
	4	20:21:20	5:20	No
	5	21:05:40	30:00	No
	6	21:37:20	17:00	No
	7	22:03:00	01:28:20	No
	8	23:31:40	01:06:20	No
	9	00:43:20	48:20	No
	10	01:33:20	13:40	No
	11	01:53:40	5:20	No
	12	02:00:40	16:40	No
	13	04:32:40	28:00	No
	14	05:02:20	10:00	No
	15	06:06:40	5:20	No
	16	08:09:00	40:20	Yes
	17	09:03:00	5:20	No
Respiration rate	18	14:09:20	5:40	No
	19	16:56:40	5:20	No
	20	17:06:40	7:40	No
	21	04:33:40	8:40	No
	22	07:34:20	7:20	No
	23	07:42:00	10:40	No
	24	07:59:20	9:00	No
	25	08:09:00	47:20	Yes

Interpretation of missing data

Several chest x-rays were performed in the 24 hours prior to the ICU readmission. What stands out, is that not all measurements are ceased during these examinations. One CT-scan was performed and this can be seen in segments 16 and 25, where all vital signs went missing for around 40 minutes and the temperature rose from 25 degrees Celsius once the recordings were resumed. This indicates that the device was detached from the patient and out of reach from the phone. These two data gaps are a clear example of escalation of care (the CT scan was ordered due to a suspected pneumothorax), in which the data is very likely to be missing not at random. All clinical signs point towards clinical deterioration and the vital signs during the scan would most likely be indicative of a further decline of the patients' health.

Case 4

In Table 13, an overview of patient demographics for this case is shown.

Table 13: Patient demographics of case 4

Age	70
Gender	Female
BMI	17.2
Medical history	Chemoradiation for squamous cell carcinoma cT4bN0M0
Surgery type	Laparoscopic esophagectomy
Type of adverse event	Emergency VATS surgery
Reason for escalation of care	Anastomotic leakage

In Figure 9, the six vital signs that were measured continuously during the 24 hours preceding the emergency surgery are shown. All manual intermittent recordings of vital signs were included in this plot.

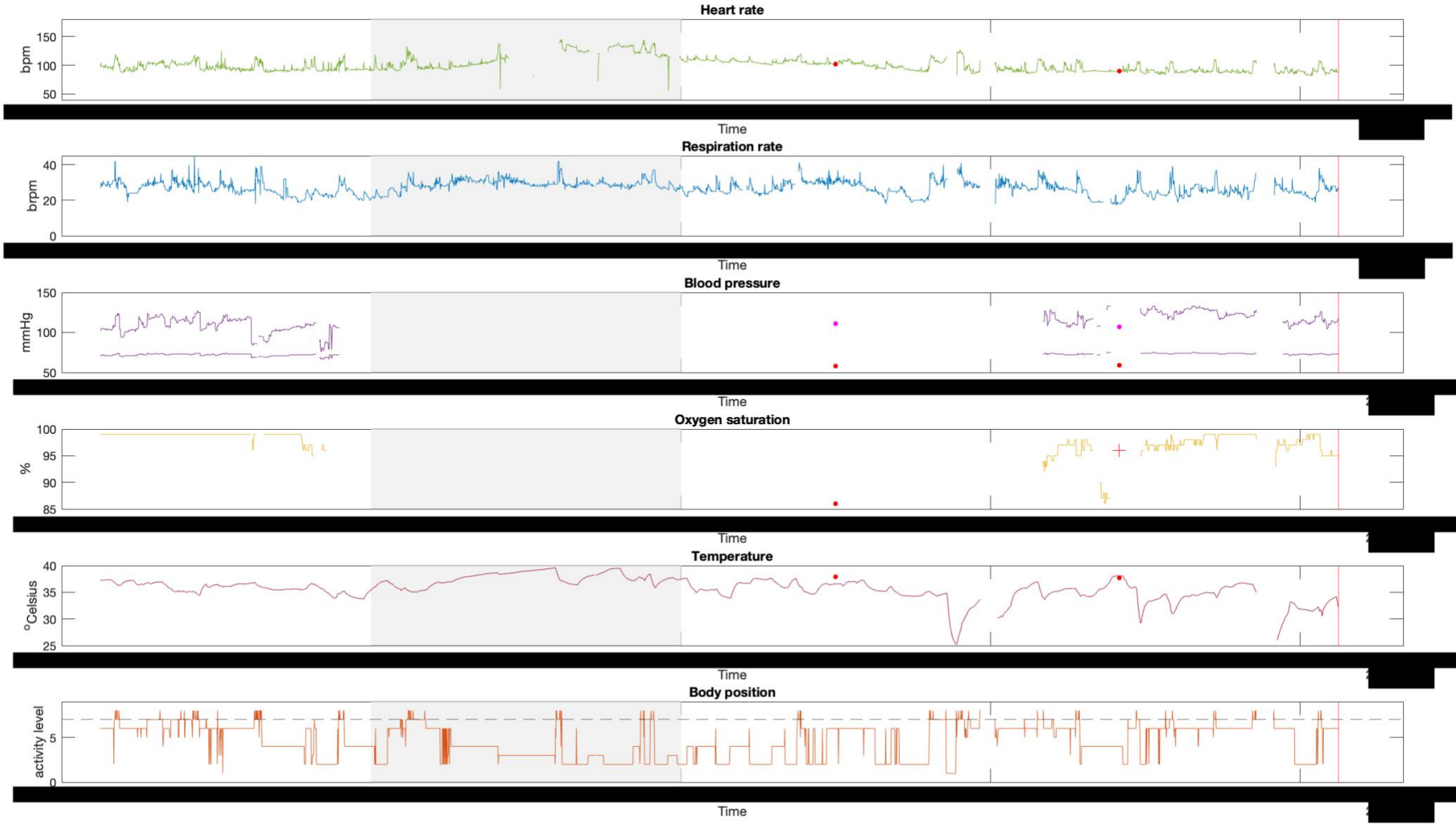

Figure 9: Continuous vital sign recordings in the 24 hours prior to the emergency VATS. The red vertical line indicates the moment the VATS was scheduled. All marks indicate manual intermittent vital sign measurements, recorded by nurses. Different shapes in oxygen saturation measurements indicate additional oxygen therapy; + = nasal cannula.

Clinical course

Eight days after the esophagectomy, this patient was preparing to go home and recover with the help of home care. As this was not available yet, she stayed in hospital for several extra days. Her clinical status was good, as she was ready to go home. She was only experiencing some dyspnea in the evening and during the night she couldn't sleep until she got temazepam to calm her down. Several hours before her emergency surgery, at 14:45, she was shivering, not feeling well and had an oxygen saturation of 86% without additional oxygen. She was increasingly dizzy and had a low tension. A chest x-ray in the morning showed a partial pneumothorax and around 17:00, a CT-scan confirmed that there was air surrounding the anastomosis and an empyema in the thorax. These findings lead to ordering the emergency VATS.

Continuous measurements

The unrest during the night can clearly be seen in the continuous measurements, with a rising temperature, and heart and respiratory rate. This is not reflected in an increased in activity, however. Over the 24 hours, respiratory rate and temperature fluctuate, while the heart rate is quite steady but high, at a minimal rate of 90 beats per minute. Oxygen saturation is steady before measurement cease at night, with a lot of saturation drops that can be seen as measurements resume around 13:00. Blood pressure measurements coincide with SpO_2 recordings, but fluctuate greatly, especially systolic blood pressure values.

Missing data

Table 14 shows the total missing percentage for each continuous vital sign, along with the amount of missing data segments and their duration, expressed in median, minimal and maximum values.

Table 14: Total percentages of missing data per vital sign in the 24 hours before the emergency VATS, the total amount of missing segments and the duration of these segments.

	Total missing (%)	***Missing segments***	***Duration segments (hh:mm:ss, median (min – max))***
Heart rate	9.2	7	00:10:40 (00:09:00 – 00:29:00)
Respiration rate	4.5	6	00:06:10 (00:01:20 – 00:16:40)
Blood pressure	62.5	15	00:03:40 (00:00:40 – 13:38:00)
Oxygen saturation	63.6	8	00:08:30 (00:00:20 – 13:53:20)
Temperature	3.1	2	00:10:30 (00:01:20 – 00:19:40)
Body position	2.6	2	00:08:40 (00:01:00 – 00:16:20)

Blood pressure and oxygen saturation have measurements less than 50% of the 24 hours, while temperature and activity levels only fail in some short instances. Missing data segments in blood pressure and respiration rate make up between 5-10% of the time.

Segments

All missing data segments with a duration of more than 5 minutes are shown in Table 15.

Table 15: All missing data segments in the continuous heart rate and respiratory rate measurements with a duration of more than 5 minutes, with their time of occurrence and duration, and information on the simultaneous loss of other vital signs. Overlapping segments are highlighted in the same colour.

Vital sign	Segment	Time	Segment duration (mm:ss)	All vital signs missing
Heart rate	1	02:40:40	27:00	No
	2	03:09:40	29:00	No
	3	04:14:20	9:20	No
	4	04:26:20	9:00	No
	5	05:48:00	10:40	No
	6	11:10:20	10:40	No
	7	11:48:40	16:40	Yes
Respiration rate	8	11:11:00	10:20	No
	9	11:48:40	16:40	Yes
	10	14:11:40	8:20	No

Interpretation of missing data

During segments 7 and 9, all vital signs went missing. This could be due to an empty battery in either the sensor or phone, or both, but seeing as measurements resume promptly 16:40 minutes later, it is more likely that the sensor was out of reach. Additionally, a chest x-ray was performed during this data gap, supporting the assumption that connectivity issues were the most likely cause here. As the chest X-ray was not part of the regular care protocol, this is categorized as escalation of care, which means this data is missing not at random. In combination with the deteriorating clinical signs from the EHR (dyspnea, too restless to sleep), this missingness in indicative of clinical deterioration.

Discussion

For each patient, data gaps were identified that were strongly suggestive of missing not at random, which means that standard missing data method - like complete case analysis – are not suitable for handling these data gaps. While some cases of data loss seemed to be missing at random, too little context information was available to confirm this suspicion. Multiple missing data segments were preceded by vital sign trends suggestive of clinical deterioration, but this was not the case for all gaps. In case of MNAR, missingness does not always have to be indicative of clinical deterioration; it could also be a sign of simply insufficient context data.

Intermittent vital signs taken by nurses are often not immediately entered into the patients EHR. With more tasks at hand, nurses often collect vitals from different patients and enter these manually after they have done their rounds in the morning. This means that certain recordings that are registered at 9:00, might have been measured somewhere in the preceding hours. While this does not have to be a problem in daily clinical practice, using it as a reference here may cause skewed comparisons when matched with the continuous measurements. New devices that automatically upload measurements into the patients' health record have been developed but are not always available at wards. Not only will this increase accuracy of measurements in the patient files, but it will also relief some of the administrative burden on nurses when functioning properly.

Different patients have different outcomes; an MC admission is different and less severe than an ICU admission. Patients' care is escalated for different reasons (mostly cardiovascular or respiratory), but due to the differences in the underlying pathological mechanisms, it can be hard to compare these. This could explain why it is difficult to detect a missingness pattern across these different patients. Pooling and matching these patterns is also hard due to the small amount of (similar) adverse events.

For the identification of missing data segments with MNAR characteristics, several extreme situations were selected through purposive sampling. While it could be argued that these MNAR segments are extreme and only happen in extreme scenarios, and focusing on these instances could introduce selection bias, the fact that these segments even occur are already sufficient to disprove the assumption of MCAR/MAR in all cases. On top of that, we are especially interested in these short periods before clinical deterioration, so it is only logical to select these specific cases.

Conclusion

For each case, several instances of missing data that were strongly indicative of MNAR have been identified. This means that it is wrong to assume data is missing (completely) at random for all missing data in continuously monitored vital signs. To handle these data gaps, more complicated methods like multiple imputation are needed to prevent introducing bias.

6. General discussion

Our study was aimed quantifying and capturing the clinical context of missing data in continuous monitoring in high-risk surgical patients on hospital wards, and using this knowledge to categorize missing data segments. This way, more knowledge on how to handle missing data was obtained.

Key findings

We found that missing data in continuous monitoring is inevitable, and data loss patterns vary greatly between vital signs and patients. Many different causes for missing data were identified, mostly relating to the usability of the sensor. Within these causes, situations where data was most likely MCAR were outnumbered by MAR and MNAR situations. In patients that experienced an adverse event, several missing data segments that were MNAR were identified, meaning that standard missing data methods are not suitable for dealing with these data gaps.

Types of remote monitoring

The Checkpoint Cardio device used for the measurements in this research was developed to perform continuous measurements, with each vital sign updating at least every second and an ECG sampled at 250 Hz. This allows for more advanced monitoring than devices that only measure heart and respiratory rate every minute. Especially the ECG provides an additional diagnostic tool, as abnormalities in heart rhythm like ventricular fibrillation (VF) can be detected. This does require more data to be transferred wirelessly and more advanced sensors, which come with drawbacks including risk of more missing data.
As can be seen in some of the patient cases, the missing data is not always the biggest limiting factor in recognizing clinical deterioration. With gaps that last between 5 and 10 minutes, nurses might not even notice data is missing during this time (unless the system would alert them). Other similar wireless monitoring systems send data once per minute or even 5 minutes, which approximately correspond to most missing data segments encountered in this research. If a real-time performance is expected, these gaps must be handled properly, but if an interval of multiple minutes is the baseline, this data loss time is simply the interval time between measurements. To select the optimal type of remote monitoring system, the patient population must be studied well, to identify what information needs to be recorded and how this balance between volumes of data and reliability of data transfer should be approached.

Sensor improvements

Several upgrades to the sensor can be made to increase usability and reliability. Heart rate could be deduced from the pulse oximetry signal if the ECG signal fails. The sensor could also be improved by adding parts that will more reliably indicate whether (a part of) the sensor is actually attached to the patient. For the temperature probe, it is apparent that it is detached if the value drops below physiological values and the patient is still alive. By using thermal resistance or conductivity measurements, the properties of the medium of which the temperature is measured can be evaluated. Furthermore, the buffer function on the sensor should be improved to accurately store data if connection to the relay device fails and upload this data as soon as connection is reestablished.

Sensor validation

It is hard to ensure an accurate golden standard alternative to validate the sensor in mobile patients. To accurately simulate real-world missing data situations, a reliable system providing measurements in case of data gaps in the wireless sensor would be needed. This system would however encounter the same problems that are faced in the Nightingale sensor, with motion artefacts and connection issues. More research should be done into validation methods for wireless sensing systems.

Recognizing clinical deterioration

Data loss is not the only problem encountered in using continuous monitoring to detect clinical deterioration. There are no criteria that define how to analyze trends, which makes it difficult to evaluate the influence of data loss on the detection of clinical deterioration. The sensor was not clinically validated, so this would need to be studied first before any prognostic models can be built on this data. Furthermore, not all deterioration events will be captured in vital signs, so they will not be enough as a standalone therapy; the clinical judgement of nurses and doctors is still very valuable.

Missing data problem

While imputation may result in acceptable reconstructions in most cases, this does not mean it will be correct to apply on an individual level. Due to regression toward the mean, of course depending on the subpopulation that is being studied, most trends of vital signs will approximately continue the same way as they did before data went missing. In the target population for continuous monitoring, when looking at the entire period that a patient would be eligible for monitoring, an adverse event is extremely rare. For the largest part, a patients' vitals will show relatively stable trends. But in the case of an adverse event, the imputed data will very likely be wrong, which can lead to overlooking an important clinical deterioration event. It is not just about providing an accurate estimate for vitals in a stable patient, which can be used to study how trends should be interpreted in the detection and prediction of clinical deterioration; the main problem is missing measurements of pathological processes at the essential moments.
If all different causes of missing data are combined, it will quickly look random and noisy, especially if the underlying causes are not related to each other. This stresses the relevance of specifying different mechanisms causing data loss and being careful with assumptions in properly dealing with missing data.

Handling missing data

We now know that handling missing data is not straightforward, but what steps should be taken to handle missing data? Van Buuren has drafted guidelines that could give some direction on how to tackle this problem. He suggests using MAR assumption as a starting point. If there is sufficient reason to suspect MNAR, more context data on the missingness of the data gaps should be collected and included in the imputation model. If the MAR assumption is still questionable, a simulation can be performed to study to what extent the MNAR mechanism can have an effect on the outcomes that are studied. He advises using a specific imputation model for MNAR and performing a sensitivity analysis. Further details can be found in his book [20].

Future perspectives

In future studies, several measures should be taken to reduce the impact of missing data. First, missing data should be minimized, through sensor improvements, integrating wireless sensors into regular care, and especially by involving doctors, nurses and patients. If they see the relevance of continuous monitoring and can experience how it can support them, it could become an important part of patient care. More patients should be included, to collect more hours of data, and more adverse events. Further research into missing data should collect more context data, to further explore causes and types of missing data, to better substantiate assumptions made in imputation models. Through clinical validation of the sensor and more research on the relationship between trends and clinical outcome, it is expected that the missing data problem will become less relevant. If we have more knowledge on trend behaviour, missingness of data could even be predicted, instead of occurring suddenly.

Furthermore, the current approach to this problem is retrospective, while a real-time solution is needed. Some studies have considered different imputation methods to handle real-time missing values, but this was applied to clinical prediction models and not data loss in continuous monitoring [28][29]. Still, this research is relevant within this context, as it also seeks to apply missing data methods in real-time [30].

In situations where even less context information is known, like home monitoring, validated sensors and more knowledge on trend data are even more important than in the hospital setting. There could be overlap in causes for missing data between remote monitoring at home and in the hospital, but further research should study the specific context of the home environment to confirm this.

General conclusion

In conclusion, missing data in continuously monitored vital signs of high-risk surgical patients is inevitable and too complex to be solved with standard missing data methods. Further research should focus on increasing our knowledge of the clinical context in which data goes missing, building imputation models around data that is missing not at random and validating these models in clinical practice to aid implementation of continuous monitoring.

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