MODERN METHODS IN VITAL SIGNS MONITORING

Harriët M.R. van Goor

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Modern methods in vital signs monitoring

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In the sum of the parts, there are only the parts
- *Wallace Stevens, On the Road Home*

In the end, it is practical, everyday medicine – what happens when the simplicities of sciences come up against the complexities of individual lives
- *Atul Gawande, Complications*

Anything easy is more trouble than it's worth
- *Tasslehoff's Mother, Dragons of Winter Night*

Assumption is the mother of all fuckups
- *Travis Dane, Under Siege 2*

The secret of change is to focus all your energy not on fighting the old, but on building the new
- *Dan Millman, Way of the Peaceful Warrior*

The aim of argument, or discussion, should not be victory but progression
- *Joseph Joubert, The Notebooks of Joseph Joubert*

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CHAPTER 1

General Introduction

If you don't take a temperature, you can't find a fever – Samuel Shem, The House of God

Vital signs are numeric measurements of essential bodily functions. The four classic vital signs are respiratory rate, heart rate, core temperature and blood pressure[1], with oxygen saturation, pain and mental status each suggested as a possible fifth or sixth[2–4]. The values of these vital signs reflect the physiological balance within the body. Consequently, aberrant vital signs reflect a (patho)physiological imbalance or balance shift. Vital signs are not independent markers of isolated processes, but rather reflect different aspects of a single process aimed to deliver oxygen from the lungs to the organs. Although influenced by each other, they do not always change simultaneously. Some vital signs will change as a physiological response to buffer deficits, such as an increased heart rate to compensate hypovolemia or an increase in respiratory rate when oxygen demand is high. Aberrations in 'regulated' vital signs, such as a low blood oxygen saturation or blood pressure, are often indicators of failing compensation[5]. Many factors can influence the overall balance. A fever for instance increases the systemic oxygen consumption[6], stimulating a rise in heart rate and respiratory rate. Iatrogenic factors, such as administered medications, can change the balance or block compensational mechanisms. For example, the administration of opioids to treat pain can cause respiratory depression, which prevents adequate ventilation[7]. Some chronic diseases cause a new balance to develop, such as a lower oxygen saturation set point in patients with chronic obstructive pulmonary disease. Correcting this 'low' SpO_2 will not improve the situation, but tips off the balance instead, and could lead to hypercapnic respiratory failure[8]. The physiological balance is patient-specific, depending on patient characteristics, disease characteristics, therapy characteristics, and circumstances.

History of vital sign measurements

Technology, documentation, and awareness are three of the elements that have influenced the measurement of vital signs in the past. Technology has made it possible for health care professionals to take objective measurements of vital signs. Although ancient physicians were already aware of the association between fever and rapid heart rate[1], the exact value of heart rate could not easily be measured at the bedside until the introduction of the pocket watch. Similarly, the development of a thermometer was needed to measure body temperature, and it was not until 1866 that a thermometer was developed that was only 15 cm long and took less than 20 minutes to take a temperature[9]. Measurement of blood oxygen saturation needed a little more technology, and the first pulse oximeter was only tested on patients in 1977[10]. Technological innovations have continued to make taking vital signs faster, easier and more accurate over time.

The second element affecting vital sign measurements is documentation. In the 19th century, organized documentation of patient information became more common, aided by the possibilities of quantitative measurements[11]. Patient records were useful to collect information more structurally, so hypotheses about disease course and therapeutic efficacy could be tested. The patient record became more professional and standardized over time, accelerated by the introduction of the Electronic Health Record (EHR) at the end of the 20th century[12]. The electronic health record expanded the capacity to utilise patient data for audits and research[13]. It also enabled authorised remote access to clinical records, supported the addition of clinical decision tools and other innovative technologies, and led to better adherence to guidelines[13,14]. Introduction of the electronic health record, with the possibility to automatically generate scores for vital signs, has shown to improve physiological surveillance and decrease in-hospital mortality[15,16]. Where technology provided us with means to measure vital signs, the electronic medical record has provided us with a means to document and re-evaluate vital signs data.

The third element discussed here is awareness. As vital signs were made more readily available by technology and documentation, the awareness of their importance grew. In the 19th century, nurse and statistician Florence Nightingale famously made nightly rounds of her patients during the Crimean war[17]. She stated that "*the most important practical lesson that can be given to nurses is to teach them what to observe..*"[18]. In her Notes on Nursing, she stresses the importance of objective and regular observations of the patient to assess his or her condition. Nonetheless, it would take another century for clinicians to recognise their prognostic significance[1].

Failure to rescue

In 1992, a landmark study was published which showed that mortality after surgical complications was more associated with hospital characteristics than patient characteristics[19]. The inability to prevent death after a complication occurred was referred to as 'failure to rescue'. Despite major improvements in health care in the previous century, there are still patients who die in the hospital, not due to their illness, but due to suboptimal management of their illness[20,21]. Researchers set out to find ways to prevent failure to rescue and unnecessary in-hospital deterioration. Early warning systems were one of the proposed solutions[22]. This system is based on the well-documented observation that serious abnormalities in vital signs can be observed eight hours before cardiac arrest or intensive care admission[23,24]. The so-called 'afferent limb' of an early warning system consists of nurses calculating an early warning score at regular intervals, which is usually based on vital signs, with predefined thresholds to determine whether action is needed[25]. The 'efferent limb' consists of the

rapid response team, which will try to correct physiological imbalances and escalate care if needed, thus improving the patient's outcome[25]. Although early warning systems have several benefits, their implementation has shown inconsistent results[26,27] due to lack of training, registration errors and poor protocol adherence[28–32]. Moreover, since early warning scores are only measured intermittently (often no more than once every 8h), periods of vital instability between measurements are easily missed[33].

To address the limitations of intermittent vital signs monitoring, technological innovation started to focus on improving the afferent limb of the early warning system, the detection of deterioration. In the past decade, wireless and wearable devices have been developed that can continuously monitor vital signs without limiting a patient's mobility[34]. These small wearable sensors come in all shapes and forms, from adhesive chest patches to wrist worn bracelets. Since continuous monitoring theoretically prevents us from missing any clinically important physiological perturbations, it was suggested it could become the ultimate solution to preventable hospital mortality[35]. Recent systematic reviews, however, found no evidence that implementation of continuous remote monitoring actually improves clinical outcomes[34,36]. No large-scale clinical trials have been published to date. Continuous wireless monitoring on hospital wards is largely still in the clinical validation and feasibility testing phase[34].

The SARS-CoV-2 pandemic

An outbreak of a new respiratory corona virus (Severe Acute Respiratory Syndrome-Corona Virus-2; SARS-CoV-2) in Wuhan, China in December 2019 quickly developed into a worldwide pandemic, which shook the world in early 2020[37]. SARS-CoV-2 causes the disease COVID-19 (COrona VIrus Disease 2019), a systemic disease with often respiratory symptoms. Although the majority of patients develops only mild disease and do not require hospitalisation, 16% of the patients at the start of the pandemic needed hospitalisation for oxygen therapy and up to 4% were admitted to the intensive care unit[38,39]. Health care organizations worldwide struggled to deliver the appropriate care to the immense number of patients with COVID-19.

The pandemic introduced new challenges. Hospital staff had to deal with a large group of patients with an unknown disease and high risk of respiratory deterioration. Simultaneously, access to patients was limited due to isolation restrictions. Furthermore, in an effort to relieve hospital capacity, patients without a direct need for oxygen therapy stayed at home as long as possible. Continuous monitoring with wearables at the general ward offered two potential advantages. Vital signs could be monitored continuously without missing periods of vital instability, possibly catching the rapid respiratory decline of COVID-19 patients early enough for intervention. Secondly, vital signs could be

monitored without the need to be in direct proximity of the patients, which was beneficial considering the contagiousness of the disease and strict isolation measures. Intermittent remote self-monitoring posed a solution to monitor and triage the large number of people at home who were not yet in need of hospital admission, but whose condition might deteriorate. Furthermore, patients could be sent home earlier under remote supervision from health care professionals, creating more hospital capacity. Consequently, during the first two years of the pandemic numerous monitoring strategies were initiated around the world, and both continuous monitoring[40–43] and monitoring at home[44–49] rapidly became part of the care for COVID-19 patients.

Standing challenges

Although innovative monitoring techniques are gaining ground, accelerated by the recent pandemic, the science of properly evaluating these techniques in their various stages of development is only just getting started. Methods-comparison studies have established which wearables produce valid measurements (and which do not) under specific circumstances, and early clinical implementation studies indicate that continuous remote monitoring on hospital wards is feasible[34]. The effect of continuous monitoring on patient outcome has mainly been assessed in observational studies of varying methodological quality. The impact of this complex intervention on other outcomes, such as the workflow of hospital staff, remains unclear. How to best process, present, use, and document the constant stream of continuous vital signs data is still unknown. Considering remote intermittent monitoring to enable remote hospital care for COVID-19 patients, most studies do describe the implementation of such an intervention, but there is a lack of high quality evidence regarding design and outcome.

We are currently at a point where a purely technical implementation of innovative monitoring techniques is often possible, but leaves us with several unanswered questions. Does (properly implemented) continuous monitoring live up to its promise of improving patient outcome and hospital work flow? How should the big data generated by continuous monitoring be used? And how can remote vital signs monitoring facilitate the transition of intramural to extramural hospital care for various patient populations?

OUTLINE OF THIS THESIS

In this thesis, we explore the challenges that arise when modern methods of vital signs monitoring are implemented in daily care. Several assumptions mentioned before will be addressed.

Part I discusses several aspects of continuous data and how to use continuous data to predict patient deterioration. In this part we aim to answer the following research questions:

- Does a circadian pattern exist in heart rate, respiratory rate and skin temperature of COVID-19 patients, and is this pattern impacted by disease severity?
- How can continuous vital signs data best be summarised to be used in practice by care givers and for predictive modelling?

In part II we explore how continuous monitoring is used by hospital staff and how it influences nurses' workflow. The research questions answered in this part are:

- How do nurses and physicians interpret continuous vital signs data?
- Does continuous monitoring limit the number of patient room visits by nurses and physicians at a COVID-19 ward?

In part III we discuss the use of remote monitoring for patients receiving hospital care at home. We aim to answer two research questions:

- Does hospital-at-home care decrease the number of days spent in the hospital for COVID-19 patients?
- What should a hospital-at-home care intervention for internal medicine patients with an infection look like, and which of these patients might benefit most from such an intervention?

The results of all three parts and implications for future research are discussed in the General Discussion.

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PART I

The use of continuous
vital signs data

CHAPTER 2

Circadian patterns of heart rate, respiratory rate and skin temperature in hospitalized COVID-19 patients

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ABSTRACT

Rationale – Vital signs follow circadian patterns in both healthy volunteers and critically ill patients, which seem to be influenced by disease severity in the latter. In this study we explored the existence of circadian patterns in heart rate, respiratory rate and skin temperature of hospitalized COVID-19 patients, and aimed to explore differences in circadian rhythm amplitude during patient deterioration.

Methods – We performed a retrospective study of COVID-19 patients admitted to the general ward of a tertiary hospital between April 2020 and March 2021. Patients were continuously monitored using a wireless sensor and fingertip pulse oximeter. Data was divided into three cohorts: patients who recovered, patients who developed respiratory insufficiency and patients who died. For each cohort, a population mean cosinor model was fitted to detect rhythmicity. To assess changes in amplitude, a mixed-effect cosinor model was fitted.

Results – A total of 429 patients were monitored. Rhythmicity was observed in heartrate for the recovery cohort ($p<0.001$), respiratory insufficiency cohort ($p<0.001$ and mortality cohort ($p=0.002$). Respiratory rate showed rhythmicity in the recovery cohort ($p<0.001$), but not in the other cohorts ($p=0.18$ and $p=0.51$). Skin temperature also showed rhythmicity in the recovery cohort ($p<0.001$), but not in the other cohorts ($p=0.22$ and $p=0.12$). For respiratory insufficiency, only the amplitude of heart rate circadian pattern increased slightly the day before (1.2 (99%CI 0.16-2.2, $p=0.002$)). In the mortality cohort, the amplitude of heart rate decreased (-1.5 (99%CI -2.6- -0.42, $p<0.001$)) and respiratory rate amplitude increased (0.72 (99%CI 0.27-1.3, $p=0.002$) the days before death.

Conclusion – A circadian rhythm is present in heart rate of COVID-19 patients admitted to the general ward. For respiratory rate and skin temperature, rhythmicity was only found in patients who recover, but not in patients developing respiratory insufficiency or death. We found no consistent changes in circadian rhythm amplitude accompanying patient deterioration.

INTRODUCTION

Many elements of human physiology follow a circadian rhythm to anticipate and react to environmental changes throughout the day[1]. Acute disruption of this cycle is associated with immune dysregulation[2], delirium[3] and even mortality at the intensive care unit (ICU)[4,5]. Hospitalization can contribute to disruption of circadian patterns due to artificial light, noise, (sedative) medication, and the fact that the individual sleep-wake cycle of a patient has to make way for the hospital routine[1]. In addition, the illness itself can cause circadian disruption, for example in the case of systemic inflammation[1,6–9]. Neuroinflammation and neurodegeneration specifically might alter the regulation genes, or clock genes, responsible for a normal 24-hour cycle. Coronavirus disease 2019 (COVID-19) has several characteristics that may lead to disruption of circadian rhythms. COVID-19 is accompanied by sleep disturbance[10], neuroinflammation[11], and in severe cases systemic inflammation and encephalopathy[12–14]. Since July 2020, patients with COVID-19 are treated with dexamethasone[15], which can affect the circadian pattern of the human metabolism depending on time of administration[16]. Moreover, circadian patterns of heart rate and respiratory rate can be disturbed by acute hypoxia[17], a common symptom of severe COVID-19.

Several vital signs have shown to follow a circadian rhythm[18–20]. Even in critically ill patients admitted to the ICU, where vital signs are highly influenced by medication and ventilation, circadian patterns were found in respiratory rate, heart rate, blood pressure and temperature[21]. Previous research in ICU settings has shown that circadian rhythm becomes increasingly more pronounced in recovering patients (who will eventually be discharged home), as opposed to patients who will not survive or were discharged with palliative care[21]. However, circadian patterns in vital signs thus far have mainly been studied in either healthy volunteers, or in critically ill patients at the ICU (where continuously recorded data is readily available). Since the development of wireless sensors, continuous monitoring of vital signs at the general hospital ward has become more common[22]. Data can be used for visual monitoring by clinicians, and for the development of clinical decision support models, to detect deterioration of patients at an earlier stage. However, the alarm strategies of many systems are mainly based on single threshold breaches. Aspects of vital sign trends, like a circadian pattern, are not considered, even though incorporating vital signs trends has the potential to improve prediction models and alarm strategies considerably[23,24]. Moreover, changes in circadian patterns themselves could be valuable predictors of deterioration. A recent study used changes in circadian rhythm characteristics to identify SARS-CoV-2 infection and predict COVID-19 diagnosis[25].

In this exploratory study, we aimed to answer three related research questions. First, we assessed whether circadian rhythms can be observed for heart rate, respiratory rate and skin temperature in COVID-19 patients admitted to a general hospital ward. Subsequently, we assessed to what extent these circadian rhythms exist in patients who develop respiratory insufficiency, patients who died, and patients who recovered without developing respiratory insufficiency. Lastly, we explored whether changes in the amplitude of circadian rhythms of vital signs can be observed in deteriorating patients, and could therefore be possible predictors of deterioration.

METHODS

We performed a retrospective cohort study of patients who were diagnosed with COVID-19. Patients were offered the chance to opt-out of retrospective data analyses during hospital registration and again at hospital discharge, according to the institutional protocol. A waiver for ethical review was obtained from the medical ethical research committee Utrecht (MERC-20-365). The study was conducted according to the principles of the Declaration of Helsinki and the General Data Protection Regulation[26,27].

Setting

During the pandemic, a continuous wireless monitoring system for vital signs was deployed at the COVID-19 cohort ward of a tertiary medical center in Utrecht, the Netherlands, starting April 1, 2020. This system recorded heart rate, respiratory rate and skin temperature twice per minute, using a wearable wireless patch sensor (Biosensor Voyage, Philips Electronics Netherlands BV) and peripheral oxygen saturation (SpO2) via a finger pulse-oximeter (EarlyVue VS30, Philips Electronics Netherlands BV). The patch sensor was attached on the left hemithorax, approximately 2 cm sub clavicular, and was replaced every three days following manufacturer instructions. Patients with a pacemaker did not receive a sensor since ECG-derived respiratory rate measurements are unreliable in paced rhythms. Heart rate, respiratory rate and oxygen saturation was real-time available for all caregivers to support care. The values for skin temperature were not directly available, since the clinical relevance of skin temperature is unsure and not yet integrated in general hospital care.

Data collection

Patients were included starting April 1, 2020 until March 1, 2021. Inclusion was stopped because the manufacturer stopped delivering these sensors to focus on the production of other sensors, but the replacement did not meet the accuracy requirements. All patients with confirmed COVID-19 and available continuous sensor data were included. To be able

to describe the cohort, baseline characteristics were recorded from the electronic patient record, including the Charlson Comorbidity Index for predicting 1-year mortality[28].

Data selection

Patients were divided into three groups: patients who recovered without experiencing respiratory insufficiency, and patients with severe clinical deterioration, divided into patients who developed respiratory insufficiency and patients who died. We chose these three groups since respiratory insufficiency and mortality are both outcomes of severe patient deterioration, but follow a different course. Patients seldom died unexpectedly, and often received palliative care in the last days before death. Therefore we decided to analyze this group separately. If a patient developed respiratory insufficiency at any point during admission, he or she was included in the respiratory insufficiency cohort, and not in the recovered cohort. If a patient developed respiratory insufficiency and died while being monitored, he or she was included in the mortality cohort instead of the respiratory insufficiency. Respiratory insufficiency was defined as the need for 15 l/min oxygen therapy, high flow oxygen therapy or mechanical ventilation, whichever came first. We did not deem ICU admission a suitable endpoint since a substantial part of the population had treatment restrictions preventing them from ICU admission, and the hospital regularly struggled with capacity problems at the ICU. Instead, we chose the endpoint hypoxic respiratory insufficiency, which better reflects the starting point of severe illness in COVID-19. The time and date of onset of respiratory insufficiency was manually collected from the electronic patient record.

Since the length of stay and length of continuous monitoring varied among patients, we chose to only include 3 days (72 hours) of data for each patient. This way we aimed to avoid overrepresentation of patients with more data. For patients in the respiratory insufficiency cohort, we selected the 72 hours before onset of respiratory insufficiency. For patients who died, we selected the 72 hours of data preceding death. Since respiratory insufficiency usually occurred within the first 72 hours (median 33 hours) of admission, we selected the first 72 hours of data for patients in the recovery group as a comparable control. Since at least 4 hours of data was needed for statistical analysis, patients with less than 4 hours of continuous data in the selected 72-hour timeframe were excluded.

All continuous vital signs data was validated before use: physiologically improbable data was removed using a predefined computer algorithm. Since our cohort included dying patients, we used wide limits for improbable data (for respiratory rate <1/min & >80/min; for heart rate <30/min & >280/min; for skin temperature < 25°C). Artifacts in respiratory rate and heart rate were filtered by removing large abrupt changes that lasted for less than 2 minutes (for respiratory rate a change of >20/min, for heart rate a change of >25/

min). To ensure we only used skin temperature data of periods that the wearable was attached to the patient, and not the data of the preparation period, we only used skin temperature data between the first and last valid heart rate measurements. The first 10 measurements (5 minutes) of skin temperature data of each patient were removed, since the sensor needed several minutes to warm up.

Statistical analysis

To limit the impact of short-lasting outliers and minutes with missing data further, the median of each vital sign per fifteen-minute segment was calculated for each patient. Subsequently we calculated the overall mean of these medians, including a 95% confidence interval (CI) and the 95% upper and lower limit of all measurements. Data was plotted for visual evaluation. For quantitative evaluation we made use of a cosinor model. A cosinor model is a type of non-linear model used to asses repetitive patterns, such as circadian rhythms[29]. A cosinor consists of several components. The MESOR (midline estimating statistic of rhythm) is the rhythm adjusted mean of the modelled variable, e.g. the rhythm adjusted mean heart rate. The amplitude is the measure of the extent of predictable change within the cycle, e.g. 2 heart beats/min. Two times the amplitude is the difference between the highest and lowest point of the cosinor regression line. The acrophase represents the timing of overall high values in a cycle, expressed in (negative) degrees, where the reference time is set to 0°, and a full period is 360°. The period is the (expected) duration of one cycle, which is 24 hours for circadian cycles. For this study, we fitted two separate cosinor models. First, we used a cosinor model of the population mean to estimate the mean coefficients of the three cohorts and to detect rhythmicity, using R package 'cosinor2' [29]. This model illustrates mean differences between the cohorts. Rhythmicity was determined by the fit of the cosinor model using the F-ratio. However, this model does not account for correlation within individual patients and cannot assess longitudinal changes in data. Therefore, we fitted a cosinor mixed effects model as second model, using R package 'cosinoRmixedeffects'[25,30]. This allows for random MESOR, amplitude and acrophase per patient. We included an interaction term with the day on which measurements were taken, to see if coefficients changed over the three-day observation period. To estimate means and mean differences, we used a bootstrapping method with 500 simulations[30]. For more elaborate explanation of this method we refer to the article by Hirten et al.[25]. A p-value of 0.01 was deemed to be statistically significant for quantitative analysis. R software version 4.0.3 (R foundation for Statistical Computing, Vienna, Austria 2021) was used for all analyses.

RESULTS

Between April 1st 2020 and March 1st 2021, a total of 429 COVID-19 patients were continuously monitored at the ward. Of these, 368 could be included for analysis: 296 patients who recovered without developing respiratory insufficiency, 27 patients who died, and 45 patients who developed respiratory insufficiency and either recovered, or died without being monitored (figure 1). Table 1 shows a description of the cohort. Note that patients who died were older, had more comorbidities, received dexamethasone less often and had a higher rate of 'Do not ventilate' orders.

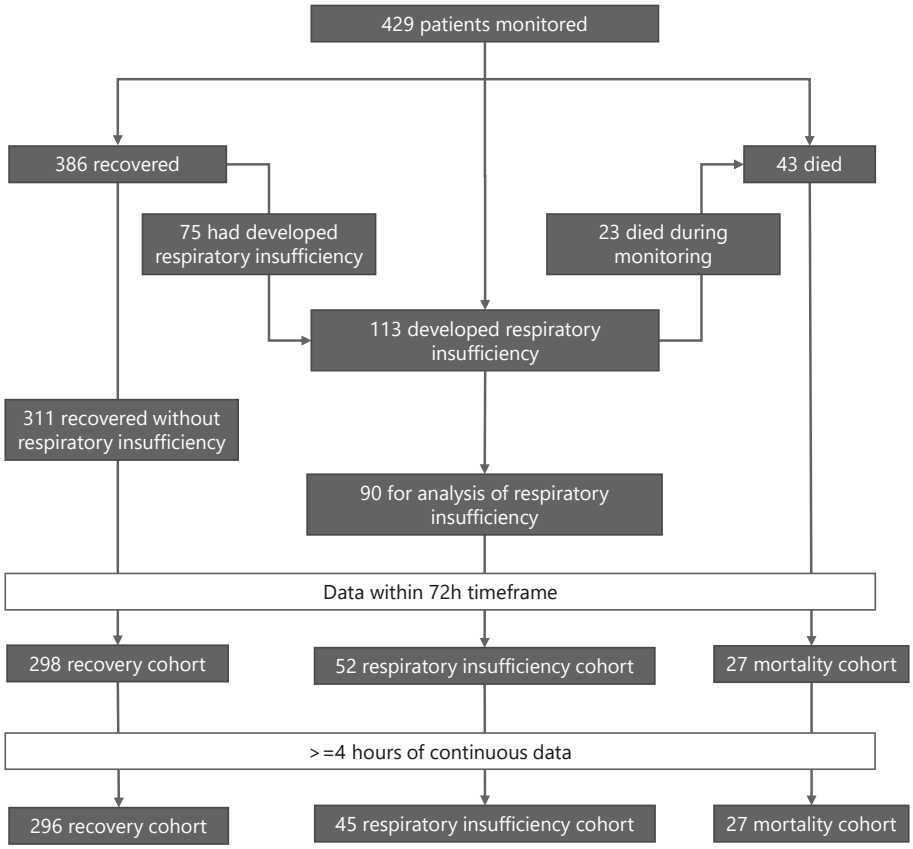

Figure 1. Flowchart of patient inclusion and data selection.

Table 1. Patient characteristics and median duration of recorded vital signs during three-day observation period.

		All	Recovery	Resp. insuf.	Mortality
Number of patients		368	296	45	27
Age (median, IQR)		65 (55-74)	63.5 (55-72)	64 (56-73)	76 (71-82)
Male sex (n, %)		221 (60.0%)	181 (61.1%)	25 (55.6%)	15 (55.6%)
CCI (median, IQR)		3 (1-4)	2 (1-4)	3 (2-4)	4 (4-6)
Dexamethasone administration (n, %)		279 (75.8%)	223 (75.3%)	38 (84.4%)	18 (66.7%)
'Do not ventilate' order (n, %)		91 (24.7%)	57 (19.3%)	10 (22.2%)	24 (88.9%)
Length of stay (median days, IQR)		7 (4-11)	6 (4-10)	15 (10-31)	8 (5-13)
Median (IQR) hours of data per patient during 72-hour timeframe	- Heart rate	72 (46.8-72)	72 (60-72)	34 (25.8-70.3)	68.8 (26.4-72)
	- Respiratory rate	62.1 (38.3-72)	63.5 (48.9-72)	31.5 (18.7-51.9)	60.5 (17.3-72)
	- Skin temperature	63.6 (37.8-63-6)	72 (52.5-72)	30.8 (12.4-51.9)	60 (15-72)

Resp. insuf.: hypoxic respiratory insufficiency, CCI: Charlson Comorbidity Index based on 1 year mortality, IQR: interquartile range.

Assessment of rhythmicity

Figure 2 shows the raw overall mean of the vital signs in the three cohorts. Both the respiratory insufficiency and mortality cohort had a small sample size and wide confidence intervals. Rhythmicity in mean heart rate was found in all cohorts (recovery $p<0.001$, respiratory insufficiency $p<0.001$, mortality p0.002) (table 2). Rhythmicity in mean respiratory rate and mean skin temperature was only found in the recovery cohort (resp. $p<0.001$ and $p<0.001$).

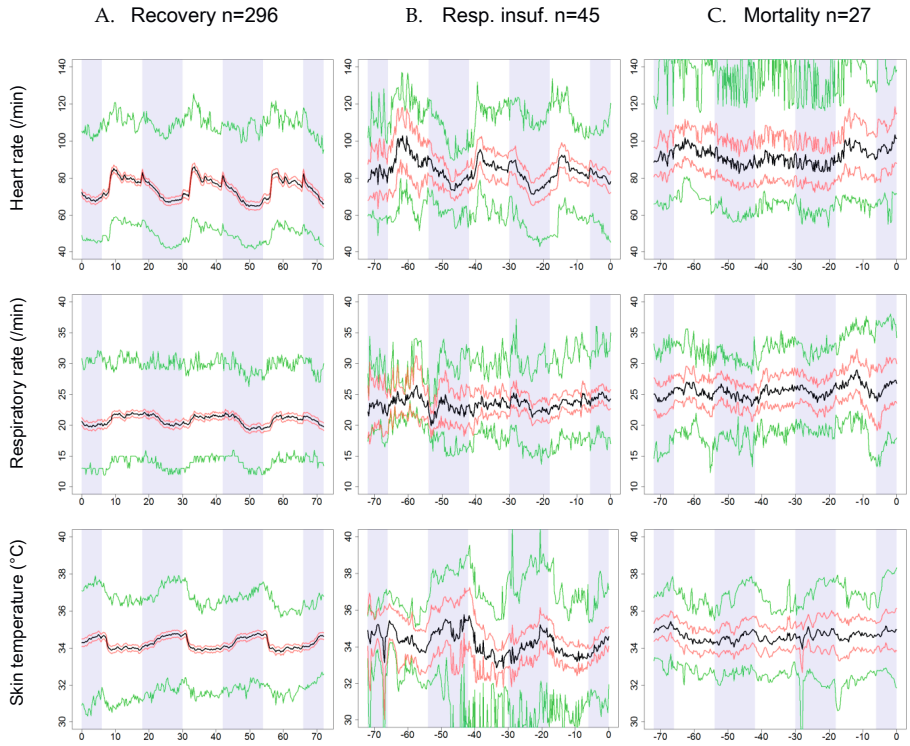

Figure 2. Mean of vital signs during three day observation period in each cohort.

X-axis: hours after first day of admission (A), before day of respiratory insufficiency (B) or before day of death (C). White panels represent time between 06.00-18.00 and blue panels represent time between 18.00-06.00. Resp. insuf.: respiratory insufficiency. Black: overal mean. Red: 95%CI of overal mean. Green: upper and lower limit of 95% range of all means.

Table 2. Coefficients of cosinor models. Recovered patients are compared to patients with respiratory insufficiency and deceased patients.

	Recovered (95%CI)	Resp. insuf. (95%CI)	p-value of difference	Died (95%CI)	p-value of difference
Heart rate (/min)					
- MESOR	74.7 (73.3-76.1)	78.9 (73.9-84.0)	0.04	95.3 (88.0-102.5)	<0.001
- Amplitude	6.9 (6.4-7.5)	5.1 (3.1-7.1)	0.76	4.0 (2.0-5.9)	0.58
» Rhythmicity	p<0.001	p<0.001		p=0.002	
Respiratory rate (/min)					
- MESOR	20.7 (20.3-211)	22.7 (21.0-24.5)	0.001	26.0 (24.4-27.6)	<0.001
- Amplitude	1.0 (0.7-1.2)	1.4 (-0.24- 2.9)	0.90	1.0 (-0.86- 3.0)	<0.001
» Rhythmicity	p<0.001	p=0.18		p=0.51	
Skin temperature (°C)					
- MESOR	34.2 (34.1-34.3)	33.2 (31.4-34.8)	0.003	34.6 (34.1-35.1)	0.07
- Amplitude	0.39 (0.28-0.50)	1.5 (-0.2 – 3.2)	0.66	0.32 (0.02-0.62)	0.95
» Rhythmicity	p<0.001	p=0.22		p=0.12	

Resp. insuf.: respiratory insufficiency, MESOR: midline estimation statistic of oscillation.

Changes in circadian pattern amplitude

The cosinor characteristics for each cohort per day are presented in figure 3 and supplemental figure 1. The MESOR values for heart rate and respiratory rate were lower in the recovery cohort than the respiratory insufficiency cohort, but higher in the mortality cohort. In the recovery cohort, an increase of amplitude was seen for all parameters over the course of the three days. The amplitude for heart rate significantly increased on day 2 (difference of 0.90 (99%CI 0.64-1.2, p<0.001)) and from day 2 to 3 (difference of 0.53 (99%CI 0.21-0.85, p<0.001)) (table 3). Respiratory rate amplitude increased from day 2 to 3 (difference of 0.25 (99%CI 0.14-0.35, p<0.001)) and skin temperature amplitude increased from day 1 to 2 (difference of 0.10 (99%CI 0.06-0.13, p<0.001). For the respiratory insufficiency cohort, only heart rate showed a clear increase in amplitude (difference day 2 to day 3 of 1.2 (0.16-2.2, p=0.002)). Skin temperature amplitude initially decreased (difference day 1 to 2 of -0.31 (99%CI -0.48- -0.14, p<0.001)) and later increased (difference day 2 to 3 of 0.16 (99%CI 0.00-0.23, p= 0.006). In the mortality cohort, heart rate amplitude decreased from day 1 to 2 (difference of -1.5 (99%CI -2.6- -0.42, <0.001), and respiratory rate amplitude increased from day 2 to 3 (difference of 0.72 (99%CI 0.27-1.3, p=0.002).

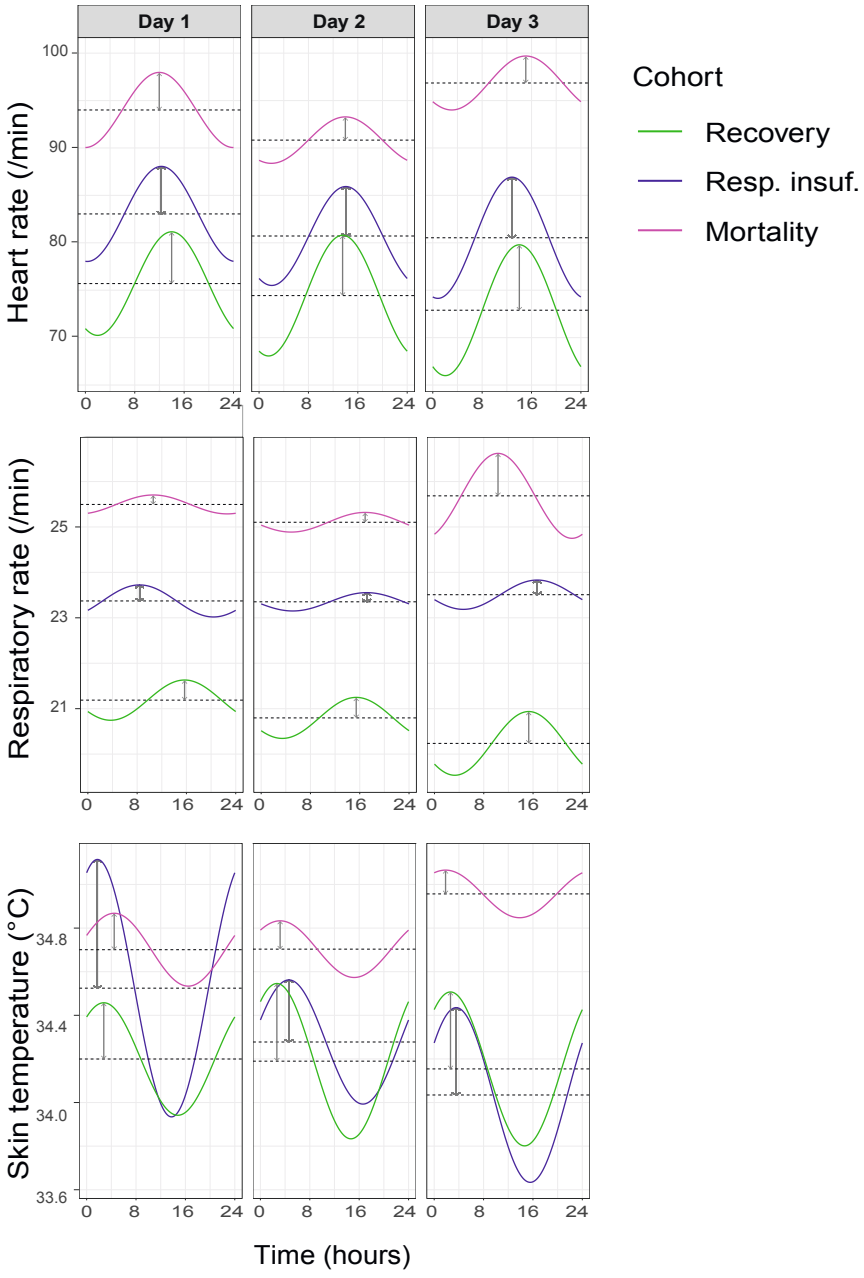

Figure 3. Progression of cosinor characteristics over the course of three days for heart rate, respiratory rate and skin temperature, stratified by cohort.

Table 3. Differences in cosinor mixed effect model amplitudes (difference, 99%CI) between days for the A. recovery cohort, B. respiratory insufficiency cohort, and C. mortality cohort.

	day 1 vs day 2	p-value	day 2 vs day 3	p-value
A. Recovery				
- Heart rate	0.90 (0.64-1.2)	<0.001	0.53 (0.21-0.85)	<0.001
- Respiratory rate	0.01 (-0.08-0.10)	0.82	0.25 (0.14-0.35)	<0.001
- Skin temperature	0.10 (0.06-0.13)	<0.001	0.00 (-0.04-0.03)	0.80
B. Respiratory insufficiency				
- Heart rate	0.20 (-1.2-1.5)	0.71	1.2 (0.16-2.2)	0.002
- Respiratory rate	-0.15 (-0.60-0.26)	0.39	0.12 (-0.19-0.49)	0.36
- Skin temperature	-0.31 (-0.48- -0.14)	<0.001	0.16 (0.00-0.23)	0.006
C. Mortality				
- Heart rate	-1.5 (-2.6- -0.42)	<0.001	0.40 (-0.75-1.6)	0.39
- Respiratory rate	0.01 (-0.34-0.35)	0.96	0.72 (0.27-1.3)	0.002
- Skin temperature	-0.04 (-0.19-0.09)	0.51	-0.02 (-0.16-0.11)	0.68

DISCUSSION

In patients admitted with COVID-19, we could confirm the presence of a circadian rhythm of heart rate. For respiratory rate and skin temperature, a circadian pattern could only be observed in patients who ultimately recovered. The amplitude of heart rate circadian rhythm increased slightly the day before respiratory insufficiency. In dying patients, a slight decrease in heart rate amplitude and an increase in respiratory rate amplitude can be observed in the days before death. Although statistically significant, these differences were small.

The existence of a circadian rhythm in vital signs has been well established[18–20]. However, in daily clinical practice, this physiological rhythm is hardly considered. With the advent of wireless continuous vital signs monitoring, patterns in vital signs are gaining attention. A recent study on cardiovascular changes in COVID-19 found a repetitive pattern in cardiovascular parameters and hypothesized this to be part of a circadian rhythm[31]. Our study confirms the existence of a circadian pattern in vital signs of hospitalized COVID-19 patients. A study performed in multiple intensive care units demonstrated circadian patterns for blood pressure, heart rate, respiratory rate and temperature[21]. This study found that the difference between the peak and nadir of vital signs is reduced in patients who died compared to patients who recovered. This led to the hypothesis that a decrease in circadian rhythm amplitude might contain prognostic information. In our study, we could not confirm a consistent decrease of circadian

rhythm amplitude in deteriorating COVID-19 patients. Some vital signs even showed a slight increase of circadian pattern amplitude during of the observation period. The method we used here, however, is different. In the study by Davidson et al., the peak-nadir excursion was used to quantify the circadian rhythm, which is somewhat different from the cosinor amplitude and might be more influenced by temporary peaks and troughs. These methodological differences might explain the observed differences in results.

Although we did not find a decrease in amplitude values for deteriorating patients, we did find a lack of rhythmicity in mean respiratory rate and mean skin temperature in the days leading up to respiratory insufficiency or death. This could be a sign of a generalized disturbed circadian rhythm in these patients. Changes in heart rate and respiratory rate during the day are mostly caused by changes in arousal and level of muscle activity, independent of the time of day[19,32–34]. If patients are active during the night, e.g. due to severe illness and/or delirium, they could have similar vital signs during these periods as during the day, resulting in a lack of rhythmicity. Periods of fever and hypoxemia could also result in temporary deviations in heart rate and respiratory rate, disrupting the circadian pattern even further.

Patients who died at the hospital ward showed no rhythmicity of respiratory rate and skin temperature, and a decrease of heart rate amplitude two days before death. This is in accordance with the observations of Davidson et al. 2021[21]. The decrease of circadian rhythm might be caused by several factors. Severe illness has shown to influence clock gene expression and melatonin excretion[35,36]. Older age is also accompanied with lower levels of melatonin[37]. Comorbidities and medication suppressing the regulation of vital signs, such as metoprolol, could have influenced circadian patterns too. Furthermore, circadian rhythms are influenced by light input[37]. As part of palliative care, patients were often relocated to single rooms with closed blinds for comfort. These patients also often received sedative medication such as opioids and benzodiazepines, blurring the difference between wake and sleep. This might have played a role in the lack of rhythmicity in this cohort. Lastly, patients often died after more than 72 hours of admission. The selected data therefore represents a later part of the admission than the data of the other two cohorts. The longer hospitalization time might have added to the disruption of circadian rhythm. In dying patients, continuous monitoring was often discontinued as part of palliative care too, so unfortunately only few patients could be included for analysis.

Skin temperature showed a circadian pattern opposite from heart rate and respiratory rate, with its peak at night instead of during the day. Core temperature usually drops during the night due to an increase of skin temperature and the subsequent excess

heat loss[38–40]. This is, however, only true for distal body parts. In our study, we used a sensor that was attached to the chest, two centimeter sub clavicular. In such a proximal location, the skin temperature is expected to follow the same pattern of the core temperature[38], instead of the inversed pattern that we observed. Why this phenomenon occurred is unknown.

Strengths and limitations

This study shows that a circadian rhythm of vital signs is present in hospitalized COVID-19 patients. All patients were admitted with the same disease, with a known pattern of deterioration, and for each patient a large set of data points was available for analysis. This made it possible to not only look at the differences between cohorts, but also to analyze more closely the changes of amplitude during deterioration. Our study also has multiple limitations. Even though the overall sample size was large, the respiratory insufficiency and mortality cohorts were relatively small, resulting in wide confidence intervals. The data selection of the mortality cohort was of a later stage of admission than the other two cohorts, introducing 'hospitalization time' as a possible confounder. In future research, this could be avoided by using a case-control design matched by length of hospital admission. Although previous studies have shown differences in vital signs patterns between men and women[21,31,41], we decided not to do a sub analysis based on sex due to the limited sample size of two of the cohorts. Secondly, all patients in our study were admitted with COVID-19, and therefore conclusions can only be drawn regarding this specific population. Lastly, skin temperature can be modified by many factors, including environmental temperature, clothing, showering, and exercise. The effect of miscellaneous factors, such as leakage of airflow from underneath an oxygen mask, are unknown. The clinical relevance and interpretation of skin temperature therefore is uncertain. Nonetheless, the observation that a circadian rhythm is present for skin temperature in COVID-19 patients who recover could be a valuable continuously measured vital parameter for the future.

Use in predictive modelling and clinical practice

Continuous monitoring is used increasingly outside high care units in an effort to detect deterioration timely[22]. In COVID-19 too, the trajectory of vital signs is hypothesized to aid in the detection of respiratory and cardiovascular decline[31]. Predictive models and alarm strategies could help clinicians to recognize deterioration, without producing too many false alarms[42]. The performance of these models might be influenced by the existence of a circadian rhythm. Previous research has already shown that accounting for differences in vital signs values between day and night may reduce alarm rate in various models at the general ward[24]. The next step in predictive modeling with continuous data is trend analysis, since changes of vital signs might be better predictors

than single values[43,44]. Both model builders and hospital professionals should be aware however that a rise in heart rate and respiratory rate in the morning, or a rise of skin temperature in the evening, might not be a deteriorating trend at all, but rather a part of a physiological rhythm. Even though this should be accounted for, changes in circadian rhythm themselves are unlikely to be useful as predictors of deterioration Lack of rhythmicity is not reflected in a decrease of amplitude, so a different metric should be used to express decrease of rhythmicity. Furthermore, one would need at least 24 hours' worth of data before being able to assess a circadian pattern. Future research should focus on adequately predicting deterioration with vital sign trends despite the existence of circadian patterns. In clinical practice, several general wards have already implemented continuous monitoring for COVID-19 patients[31,45,46]. Alarm strategies and escalation protocols are often based on early warning scores, which could be influenced by physiological changes in vital signs over the day. Based on our clinical experience during the pandemic, the early warning scores of the majority of COVID-19 patients increase in the morning when patients become physically active. Awareness of the existence of a circadian rhythm in common vital signs might aid nurses and physicians in the interpretation of continuous data and continuous early warning scores.

CONCLUSION

In conclusion, a circadian rhythm is present in heart rate of COVID-19 patients admitted to the general ward. For respiratory rate and skin temperature, rhythmicity was only found in patients who recovered, but not in patients developing respiratory insufficiency or death. We found no consistent changes in circadian rhythm amplitude accompanying patient deterioration.

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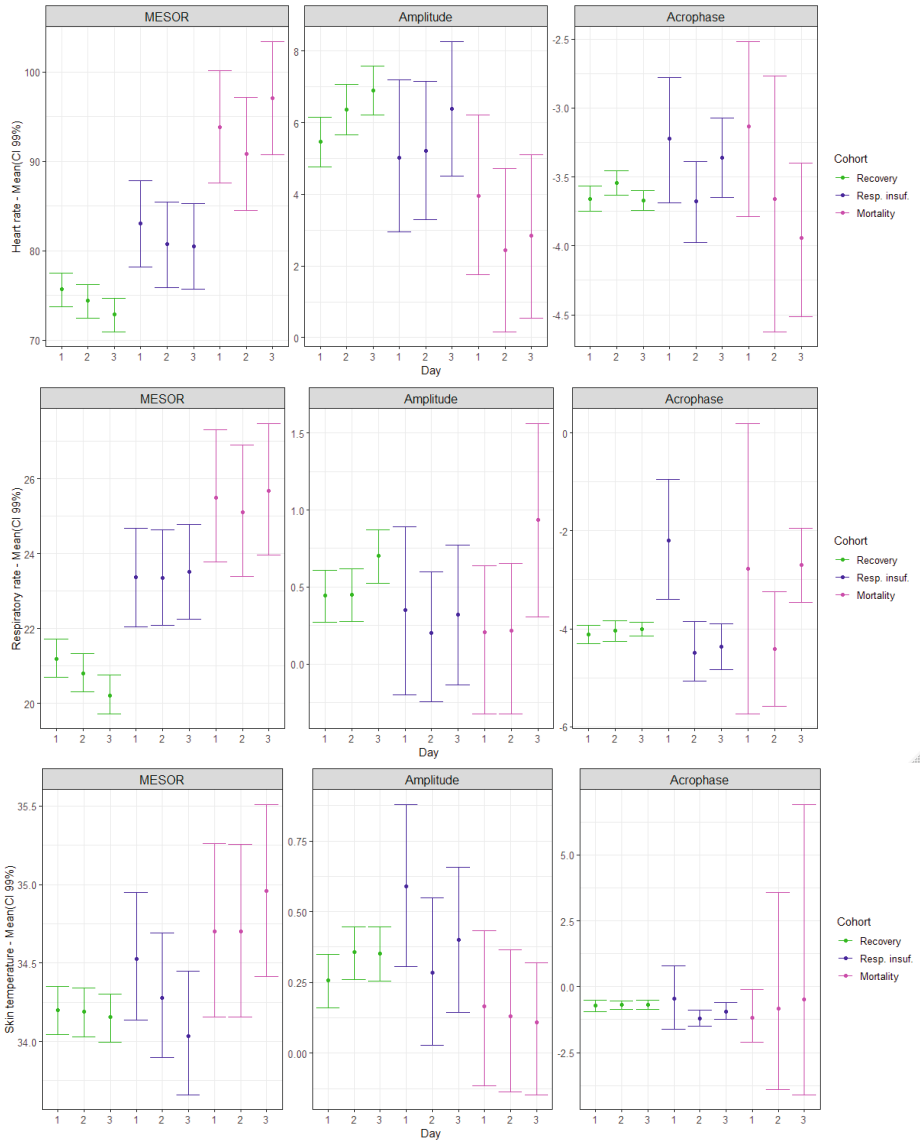
SUPPLEMENTAL MATERIAL



Supplemental figure 1. Progression of cosinor characteristics per vital sign per group, mean with 99%CI. MESOR: midline estimation statistic of rhythm. MESOR and amplitude are in /min for heart rate and respiratory rate, and °C for skin temperature. Acrophase in ° (degree).

CHAPTER 3

Continuously measured vital signs and their association with respiratory insufficiency in hospitalised COVID-19 patients: a retrospective cohort study

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ABSTRACT

Background – Continuous monitoring of vital signs has the potential to assist in the recognition of deterioration of patients admitted to the general ward. How to efficiently process and use continuously measured vital signs data is still unknown. In this study we explore methods to summarise continuously measured vital signs data, and evaluate their association with respiratory insufficiency in COVID-19 patients at the general ward.

Methods – In this retrospective cohort study, we included patients admitted to a designated COVID-19 cohort ward equipped with continuous vital signs monitoring. We collected continuously measured data of respiratory rate, heart rate and oxygen saturation. For each patient, 7 methods to summarise vital signs data were calculated: mean, slope, variance, occurrence of a threshold breach, number of episodes, and total duration and area above/under a threshold. These summary measures were calculated over timeframes of either 4 or 8 hours, with a pause between the last data point and the endpoint (the 'lead') of 4, 2, 1 or 0 hours, and with 3 predefined thresholds per vital sign. The association between each of the summary measures and the occurrence of respiratory insufficiency was calculated using logistic regression analysis.

Results – Of the 429 patients that were monitored, 334 were included for analysis. Of these, 66 patients developed respiratory insufficiency (19.8%). Summarised continuously measured vital signs data in timeframes close to the endpoint showed stronger associations than data measured further in the past (i.e. lead 0 vs. 1, 2 or 4 hours), and summarised estimates over 4 hours of data had stronger associations than estimates over 8 hours of data. The mean was consistently strongly associated with respiratory insufficiency for the three vital signs: in a 4-hour timeframe without a lead, the standardised odds ratio for heart rate was 2.59 (99%CI 1.74-4.04), for respiratory rate 5.05 (99%CI 2.87-10.03), and for oxygen saturation 3.16 (99%CI 1.78-6.26). The strength of associations of summary measures varied per vital sign, timeframe and lead.

Conclusion – The mean of a vital sign showed a relatively strong association with respiratory insufficiency for the majority of vital signs and timeframes. The type of vital sign, length of the timeframe and length of the lead influence the strength of associations. Highly associated summary measures and combinations could be used in a clinical prediction score or algorithm for an automatic alarm system.

INTRODUCTION

Hypoxic respiratory failure is a common complication of COVID-19, caused by severe viral pneumonia or concomitant pulmonary embolism[1,2]. Respiratory deterioration can occur suddenly and sometimes without signs of dyspnea[3,4], which complicates detection. Tools to assess vital instability of patients more frequently could help to detect respiratory deterioration in time. Currently, most hospitals use a form of early warning score as 'track-and-trigger' system at the general ward to aid health care professionals in the detection of deterioration[5]. Early warning scores can vary from scores with a few physiological parameters, such as the Modified Early Warning Score[6], to machine-learning algorithms including baseline patients characteristics and laboratory results[7]. However, these models use intermittent measurements to update their prediction, and are therefore limited by the frequency of spot check measurements and laboratory tests.

An alternative strategy to improve early detection of deterioration could be continuous monitoring including assessment of vital signs. Continuous monitoring can be beneficial in two ways. First, trends in vital signs over time have shown to have higher predictive accuracy than isolated vital sign values when incorporated in prediction models[8,9]. With continuous monitoring, trends in vital signs are available at any point in time, and can therefore be used to make up-to-date predictions more frequently. Unfortunately, prediction models using continuously measured vital signs data at the general ward are not yet readily available for clinical use. A second benefit of continuous monitoring is that it enables health care professionals to access the real-time vital sign status of a patient remotely, and to use this information in clinical decision making[10]. However, nurses and physicians at low care wards are usually not used to, or trained in, evaluating continuous vital signs data[11]. Current practice is therefore mostly based on experience and expert opinion. Knowledge of 'what to look for' in vital sign trends could aid nurses and physicians to interpret continuously measured data in a meaningful way.

In this study, we assessed several measures to summarise continuously measured vital signs data, and evaluated their association with respiratory insufficiency in COVID-19 patients admitted to the general ward. We aimed to find summary measures which could be clinically helpful to recognise respiratory deterioration early, and which might be useful to incorporate into an algorithm for automatic alarming.

METHODS

Population and Setting

At the beginning of April 2020, a continuous wireless system for vital signs monitoring was introduced at the COVID-19 cohort ward of the tertiary hospital University Medical Center Utrecht, Utrecht, the Netherlands. This system recorded heart rate (HR) and respiratory rate (RR) using a validated wireless patch sensor[12] (Biosensor Voyage, Philips Electronics Netherlands BV), and peripheral oxygen saturation (SpO2) via a finger pulse-oximeter (EarlyVue VS30, Philips Electronics Netherlands BV), every 30 seconds approximated over the past 30 seconds. Data was stored in software program AnStat (CarePoint Nederland BV, Ede, The Netherlands). Pulse-oximeters were delivered later than the wearable sensors (end of May 2020). We included patients from April 2020 until March 1, 2021. Patients were included if they were ≥18 years old, diagnosed with COVID-19, and continuously monitored during their admission at the study ward (either with the Biosensor, pulse-oximeter, or both). Patients with a pacemaker did not receive a sensor since RR measurements are unreliable in paced rhythms. All continuously measured data was real-time available for hospital staff, without a predefined protocol on how to use continuously measured data or how to detect respiratory insufficiency. The protocol in use for detecting deterioration in general was the National Early Warning Score (NEWS) 2[13]. The updated Charlson Comorbidity Index was used to assess baseline risk of 1-year mortality[14].

Ethical considerations

The study was conducted according to the principles of the Declaration of Helsinki and the General Data Protection Regulation[15,16]. Ethical review was waived by the medical ethical committee Utrecht (MEC-20-365). Patients were offered the chance to opt-out of retrospective data analyses during hospital registration and again at hospital discharge, according to the institutional protocol. Data was previously used in a study of circadian rhythm in continuously measured vital signs[17].

Primary Endpoint

The primary endpoint was respiratory insufficiency, which we defined as the need for 15L/min oxygen, high flow nasal oxygen therapy or mechanical ventilation, whichever came first. We did not deem intensive care unit (ICU) admission or death a suitable endpoint since a substantial part of the population had treatment restrictions preventing them from receiving cardiac resuscitation, mechanical ventilation and/or ICU admission. Moreover, high flow nasal oxygen therapy was also given at the general ward, since ICU beds were not always available. The first documentation of the endpoint in the electronic patient record was used as time point for respiratory insufficiency.

Data Selection

For each patient we selected 12 hours of continuous vital signs data. For patients who became respiratory insufficient, we selected the 12 hours of data prior to the onset of respiratory insufficiency. The distribution of the timing of reaching the endpoint in our cohort was around 40 hours after start monitoring, with a right skewed distribution (so a lot of cases reach respiratory insufficiency before this 40-hour point). For patients who did not reach this endpoint, we selected the data from 24 hours up to 36 hours after admission (figure 1). We chose this window since the majority of patients was connected to the monitoring system within 24 hours after admission. Moreover, the median time until respiratory insufficiency in our cohort was 40.6 hours (IQR 22.6-70.4) after start monitoring with a right skewed distribution. By selecting 24-36 hours after start monitoring for the control group, the timing for the timeframes for both the endpoint and control group were fairly similar. Potential artefacts (RR <1/min or >80/min, HR <30/min or >280/min, SpO2 <50%, and large abrupt changes in RR (>20 breaths/min) and HR (>25 beats/min) that lasted for less than 2 minutes) were removed. For each patient, we divided the selected data of 12 hours into 8 different timeframes of either 4 or 8 hours long (figure 1). We chose these lengths because they clinically correlate with the length of a usual half and full shift of hospital professionals. In addition, we shifted timeframes either 0, 1, 2 or 4 hours from the end of the selected 12-hour data window (the 'lead') (figure 1). With a lead of e.g. 4 hours, we assessed whether associations could already be observed 4 hours before the onset of respiratory insufficiency. To handle missing data, timeframes were only included if the first measurement of a timeframe was within 30 minutes of the start of the timeframe, and the last measurement was within the last 30 minutes of the timeframe. We did this to avoid selection of timeframes that were actually smaller than assumed due to missing data (e.g. if a timeframe of 8 hours only contains 5 hours of data, it is not actually an 8-hour timeframe but a 5-hour timeframe).

Selection of Summary Measures

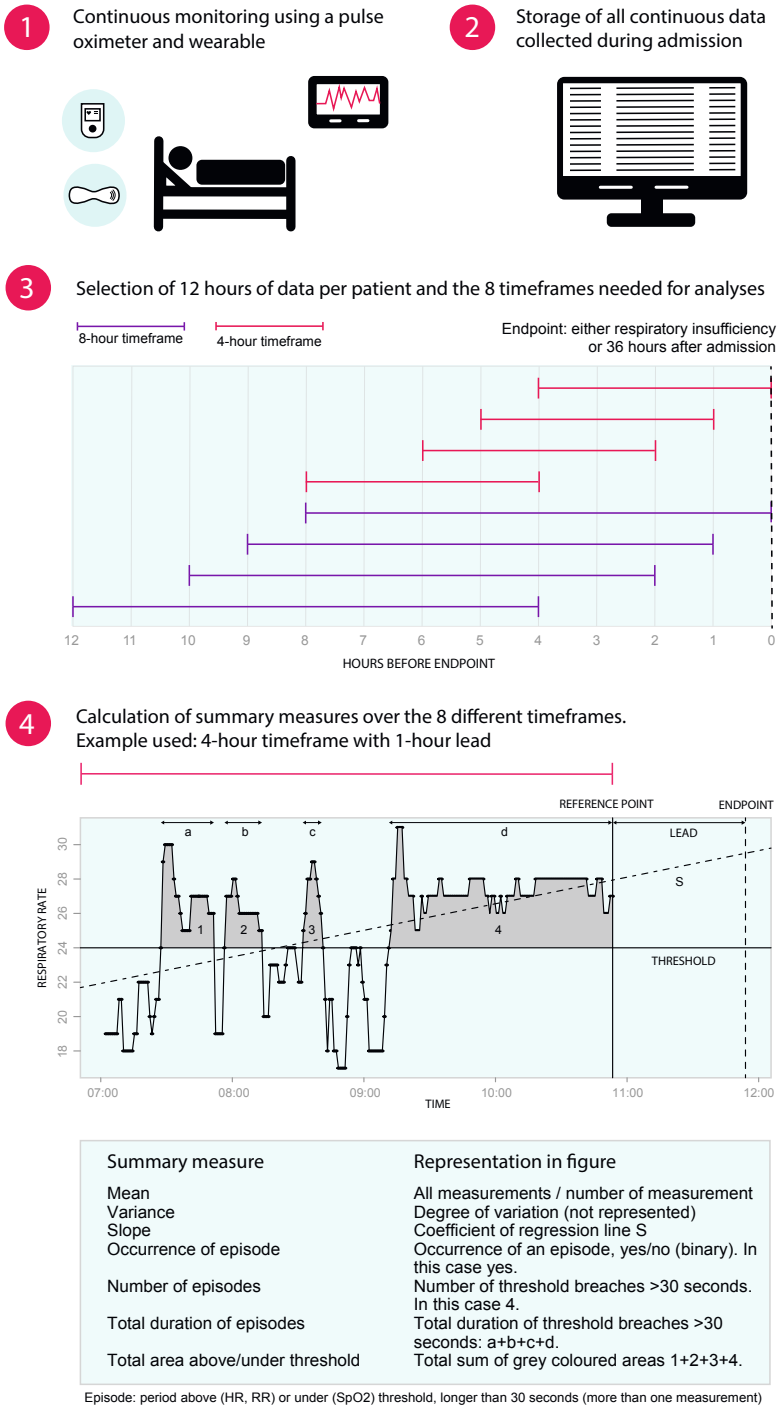
As the continuous monitoring of vital signs provide measurements twice every minute, we summarised the continuously measured data into 'summary measures'. Summary measures are either unrelated to a certain threshold (e.g. the mean HR), or related to a threshold (e.g. duration of HR >89/min). For all threshold related variables, we chose three thresholds per vital sign. Thresholds for HR were based on the three upper thresholds for tachycardia of the NEWS2, >90/min, >110/min, and >130/min[13]. For tachypnea we used the upper two levels of the NEWS2, >20/min and >24/min, and added a third one, >30/min, since the first upper threshold of the NEWS2 would be met by almost every COVID-19 patient. We used the lower two levels of SpO2, <94% and <92%, and added <90% for similar reasons. We chose not to include bradycardia or bradypnea since bradycardia and bradypnea were very uncommon as signs of respiratory insufficiency in our population.

An episode was defined as more than one measurement (longer than 30 seconds) above or below a certain threshold. Initially we defined 12 summary measures based on literature and clinical reasoning[8,18] (supplemental table 1). Correlation plots of these summary measures showed high correlation between several measures. The summary measure 'standard deviation' showed high correlation with 'variance' and was therefore eliminated. 'Mean duration', 'maximum duration' and 'total duration' above/under the threshold were highly correlated, therefore we only included 'total duration'. A similar choice was made for area above/under the threshold. Ultimately, we selected seven summary measures for analysis: three summary measures unrelated to a threshold and four summary measures related to a threshold (figure 1).

Statistical Analysis

Baseline characteristics were described for both cohorts. For every patient, all selected summary measures were calculated for the eight timeframes. To investigate the crude association between each of the summary measures and the development of respiratory insufficiency, univariable logistic regression was performed. Effect estimates were reported as odds ratios (OR) with accompanying confidence intervals (CI). Since the mean and slope of SpO2 have a negative relationship with the endpoint (a decrease in oxygen saturation is associated with the endpoint instead of an increase), the inverse effect estimate was reported for these two summary measures of SpO2. As the selected summary measures had different units of measurement (e.g. duration in minutes, area above the threshold in /min*duration or %*duration), we could not directly compare their associated with each other based on crude odds ratios. Therefore, we used standardised odds ratios (sOR) to compare the association of different summary measures with respiratory insufficiency on a similar magnitude. Standardised summary measures for each patient were calculated by using the formula $Z=(x-\mu)/\sigma$, where Z is the newly computed standardised value, x is the summary measure for a particular patient, μ is the mean of the same summary measure for all patients in this timeframe, and σ is the standard deviation of all patients in the respective timeframe. With these standardised measured, the sORs were calculated. For example, a sOR of 2 for a certain summary measure means that if the standard deviation of this measure increases by one, the association with respiratory insufficiency increases with two.

To take multiple testing into account, we tested against a p-value of 0.01 for all aforementioned analyses. Bonferroni adjustment was deemed too conservative since the chosen summary measures are highly dependent on each other. We used R software version 4.0.3 (R foundation for Statistical Computing, Vienna, Austria 2021) for all analyses.



Summary measure	Representation in figure
Mean	All measurements / number of measurement
Variance	Degree of variation (not represented)
Slope	Coefficient of regression line S
Occurrence of episode	Occurrence of an episode, yes/no (binary). In this case yes.
Number of episodes	Number of threshold breaches >30 seconds. In this case 4.
Total duration of episodes	Total duration of threshold breaches >30 seconds: a+b+c+d.
Total area above/under threshold	Total sum of grey coloured areas 1+2+3+4.

Episode: period above (HR, RR) or under (SpO2) threshold, longer than 30 seconds (more than one measurement)

Figure 1. Data selection for continuous heart rate, respiratory rate and oxygen saturation.

RESULTS

The description of the cohort can be found in table 1. Of the 429 patients that were monitored, 334 were included for analysis (figure 2), 66 of whom developed respiratory insufficiency (19.8%). These patients more often had pulmonary embolism, ICU and medium care unit admissions, treatment restrictions, and had higher mortality rates (table 1). Two patients who did not experience respiratory insufficiency were shortly admitted to a high care unit during monitoring: one patient required monitoring for severe hypokalaemia, the other patient suffered a stroke and was admitted for thrombolysis. All patients had available HR data. The sample of patients with RR data was smaller (n=288) since the sensor had to be calibrated to measure RR, which was not always executed immediately. Due to late delivery and incompliance of patients with the pulse oximeter, only 238 had available SpO2 data. On baseline, these samples differed slightly in number of patients that received dexamethasone and number of patients that reached the endpoint (supplemental table 2). Overall, patients who developed respiratory insufficiency had a higher occurrence of threshold breaches, and spent more time above thresholds for HR and RR and under the thresholds for SpO2 in both 4-hour and 8-hour timeframes (supplemental table 3a/3b). The mean number of measurements per hour was 79 for 4-hour timeframes and 74 for 8-hour timeframes. Of all timeframes used, 98,8% contained at least 120 measurements.

Association of Summary Measures with Respiratory Insufficiency

Since the highest crude OR's were observed in the 4-hour timeframe without a lead, we have outlined the results of the analysis for this timeframe in table 2. The summary measure with the highest crude OR was the occurrence of RR >24/min (OR 13.8, 99% 3.68-103.4) (table 2). For many summary measures of RR and SpO2, confidence intervals were extremely wide, in particular in summary measures that were threshold dependent and for which the threshold is breached by the majority of the patients in an outcome group. For example, a threshold breach for SpO2 of <90% occurred in all but one cases of patients who experienced respiratory insufficiency. This lead to a 99%CI of 1.64-915.0. This phenomenon was seen in other timeframes, too. When comparing the standardised OR's in the 4-hour timeframe without a lead, we found stronger associations for RR and SpO2 than HR. The mean showed a strong association for all three vital signs, with an sOR of 2.59 (99%CI 1.74-4.04) for HR, 5.05 (99%CI 2.87-10.03) for RR, and 3.16 (99%CI 1.78-6.26) for SpO2 (supplemental figure 1).

Table 1. Baseline characteristics and summary of available data.

	All (n=334)	No resp insuf (n=268)	Resp insuf (n=66)
Age (median, IQR)	65 (55.3-73.8)	63 (55-72)	67 (60-75)
Male sex (n, %)	207 (62.0%)	168 (62.7%)	39 (59.1%)
Charlson Comorbidity Index (median, IQR)	0 (0-1)	0 (0-1)	0 (0-2)
Dexamethasone during admission (n, %)	262 (78.4%)	208 (77.6%)	54 (81.8%)
Diagnosed with pulmonary embolism (n, %)	24 (7.2%)	14 (5.2%)	10 (15.2%)
Treatment restrictions[a] (n, %)	91 (27.2%)	62 (23.1%)	29 (43.9%)
Length of hospital stay (median, IQR)	7 (5-12)	6.5 (4.8-10)	13 (9-24)
ICU or MCU admission (n, %)[b]	57 (17.1%)	30 (11.2%)	27 (40.9%)
Mortality (n, %)	23 (6.9%)	2 (0.7%)	21 (31.8%)
Heart rate			
Patients with available data (n,%)	334 (100%)	268 (100%)	66 (100%)
Mean duration per patient (hours, SD)	11.7 (1.1)	11.8 (0.8)	11.4 (1.7)
Respiratory rate			
Patients with available data (n, %)	288 (86.2%)	231 (86.2%)	57 (86.4%)
Mean duration per patient (hours, SD)	11.6 (1.4)	11.7 (1.1)	11.1 (2.1)
Peripheral oxygen saturation			
Patients with available data (n, %)	238 (71.3%)	184 (68.7%)	54 (81.8%)
Mean duration per patient (hours, SD)	11.4 (1.4)	11.5 (1.1)	10.9 (2.1)

Resp insuf: combined endpoint of respiratory insufficiency, IQR: inter quartile range, ICU: intensive care unit, MCU: medium care unit, SD: standard deviation.

[a]Treatment restrictions: no resuscitation, no ventilation, and/or no ICU admission.

[b]If a patient was monitored after ICU admission and did not reach the endpoint while being monitored, he/she was included in the 'no respiratory insufficiency' group.

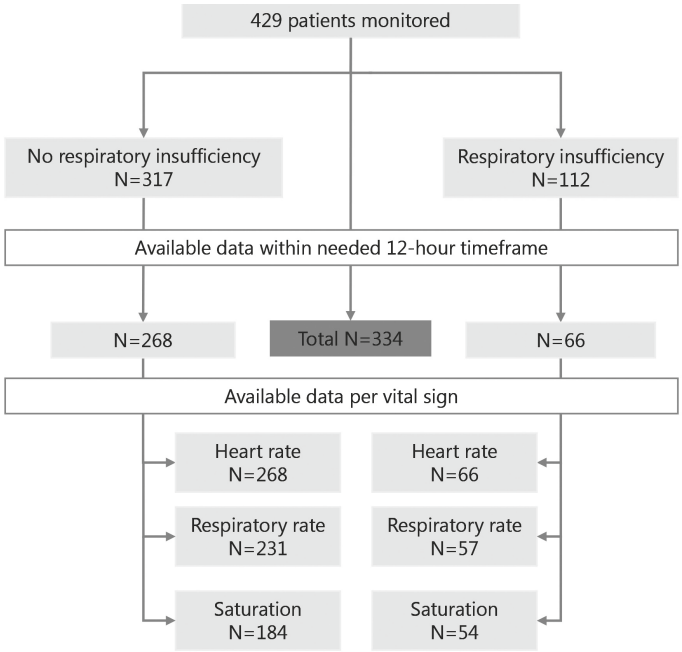


Figure 2. Flowchart of patient selection based on data availability.

Table 2. Result of univariable, not standardised, analyses for 4 hour timeframes without a lead.

Parameter	Threshold	Summary measure	OR	99%CI	p-value
Heartrate	None	Mean (/min)	1.06	1.03-1.08	<0.001
		Slope (/min/hour)	1.02	0.92-1.12	0.64
		Variance (/min^2)	1.00	0.99-1.00	0.99
	>90/min	Occurrence	4.50	1.95-11.8	<0.001
		Number of episodes	1.12	1.03-1.23	<0.001
		Total duration (min)	1.01	1.01-1.01	<0.001
		Total area above threshold (/10min)	1.00	1.00-1.01	<0.001
	>110/min	Occurrence	2.79	1.24-6.18	<0.001
		Number of episodes	1.16	1.02-1.35	0.005
		Total duration (min)	1.01	1.00-1.03	0.002
		Total area above threshold (/10min)	1.00	1.00-1.01	0.036
	>130/min	Occurrence	6.09	1.56-25.5	<0.001
		Number of episodes	1.98	1.04-5.01	0.029
		Total duration (min)	1.01	1.00-1.04	0.082
		Total area above threshold (/10min)	1.00	0.99-1.02	0.37

Table 2. (Continued)

Parameter	Threshold	Summary measure	OR	99%CI	p-value
Respiratory rate	None	Mean (/min)	1.44	1.27-1.67	<0.001
		Slope (/min/hour)	1.30	0.88-1.93	0.086
		Variance (/min^2)	1.09	1.01-1.17	0.003
	>20/min	Occurrence	7.35	1.03-531.0	0.053
		Number of episodes	0.89	0.77-1.01	0.028
		Total duration (min)	1.02	1.01-1.03	<0.001
		Total area above threshold (/10min)	1.04	1.02-1.05	<0.001
	>24/min	Occurrence	13.8	3.68-103.4	<0.001
		Number of episodes	1.21	1.09-1.35	<0.001
		Total duration (min)	1.02	1.01-1.03	<0.001
		Total area above threshold (/10min)	1.05	1.03-1.08	<0.001
	>29/min	Occurrence	8.53	3.63-21.2	<0.001
		Number of episodes	1.59	1.32-1.98	<0.001
		Total duration (min)	1.02	1.01-1.04	<0.001
		Total area above threshold (/10min)	1.07	1.03-1.13	<0.001
Oxygen saturation	None	Mean (%)	1.61	1.27-2.04	<0.001
		Slope (%/hour)	1.79	0.90-3.70	0.033
		Variance (%^2)	1.21	1.09-1.38	<0.001
	<94%	Occurrence	12.6	4.11-47.7	<0.001
		Number of episodes	1.30	1.11-1.56	<0.001
		Total duration (min)	1.05	1.02-1.09	<0.001
		Total area under threshold (/10min)	0.80	0.67-0.91	<0.001
	<92%	Occurrence	12.3	3.07-94.5	<0.001
		Number of episodes	1.30	1.15-1.49	<0.001
		Total duration (min)	1.03	1.02-1.05	<0.001
		Total area under threshold (/10min)	0.88	0.82-0.94	<0.001
	<90%	Occurrence	11.9	1.64-915.0	0.017
		Number of episodes	1.09	1.01-1.19	0.006
		Total duration (min)	1.02	1.01-1.03	<0.001
		Total area under threshold (/10min)	0.93	0.90-0.96	<0.001

Summary Measures for Heart Rate

The highest standardised ORs were observed for mean HR in the 4-hour timeframe without a lead (sOR 2.59, 99%CI 1.75-4.04) (figure 3). Only three summary measures were significantly associated with respiratory insufficiency in all timeframes: the mean, the total duration >90/min, and the total AAT >110/min. In general, associations were stronger for summary measures in 4-hour timeframes compared to 8-hour timeframes. A notable exception was the slope, for which the associations were low or insignificant in three 4-hour timeframes, but relatively strong in the 8-hour timeframes. Differences in sOR's between leads were small for most summary measures.

Summary Measures for Respiratory Rate

The highest standardised ORs were observed for mean RR (sOR 5.05, 99%CI 2.87-10.03) and the total duration of RR >20/min (sOR 4.69, 99%CI 2.55-10.29) in the 4-hour timeframe without a lead (figure 4). For most threshold dependent summary measures, the strength tended to decline when the lead increased, but still reached significance. Summary measures calculated over 4-hour timeframes had stronger associations than 8-hour timeframes. Remarkably, the number of episodes >20/min was negatively associated with respiratory insufficiency, probably because in order to have multiple episodes above 20/min, a patient would also need periods of time with a RR under 20/min, something that most deteriorating patients didn't show.

Summary Measures for Oxygen Saturation

For SpO2, confidence intervals were generally wider due to the smaller sample size. The strongest association was found in the 8-hour timeframe without a lead, for occurrence of SpO2 <90% (sOR 4.74, 99%CI 2.36-13.23) (figure 5). SpO2 was the only vital sign for which associations were generally slightly stronger in 8-hour timeframes. For many summary measures, the association with respiratory insufficiency was evidently stronger in the timeframes without a lead, especially for variance, total duration and total AUT. The mean showed a weaker association than some threshold related summary measures, e.g. occurrence of SpO2<94% in 4-hour timeframes. Nonetheless, the mean was significantly associated with respiratory insufficiency in all timeframes.

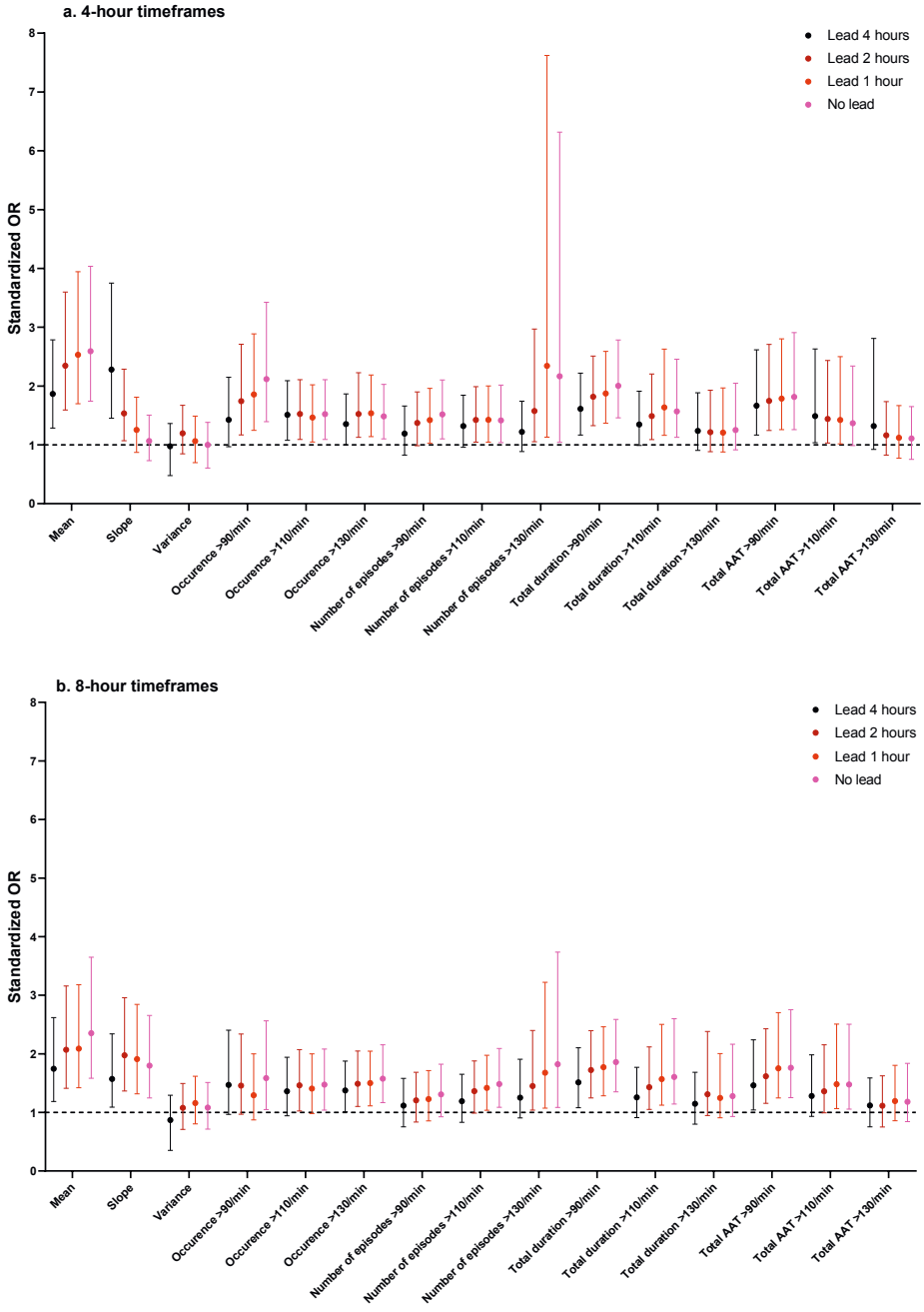


Figure 3. Standardised odds ratio's (OR) for heart rate.

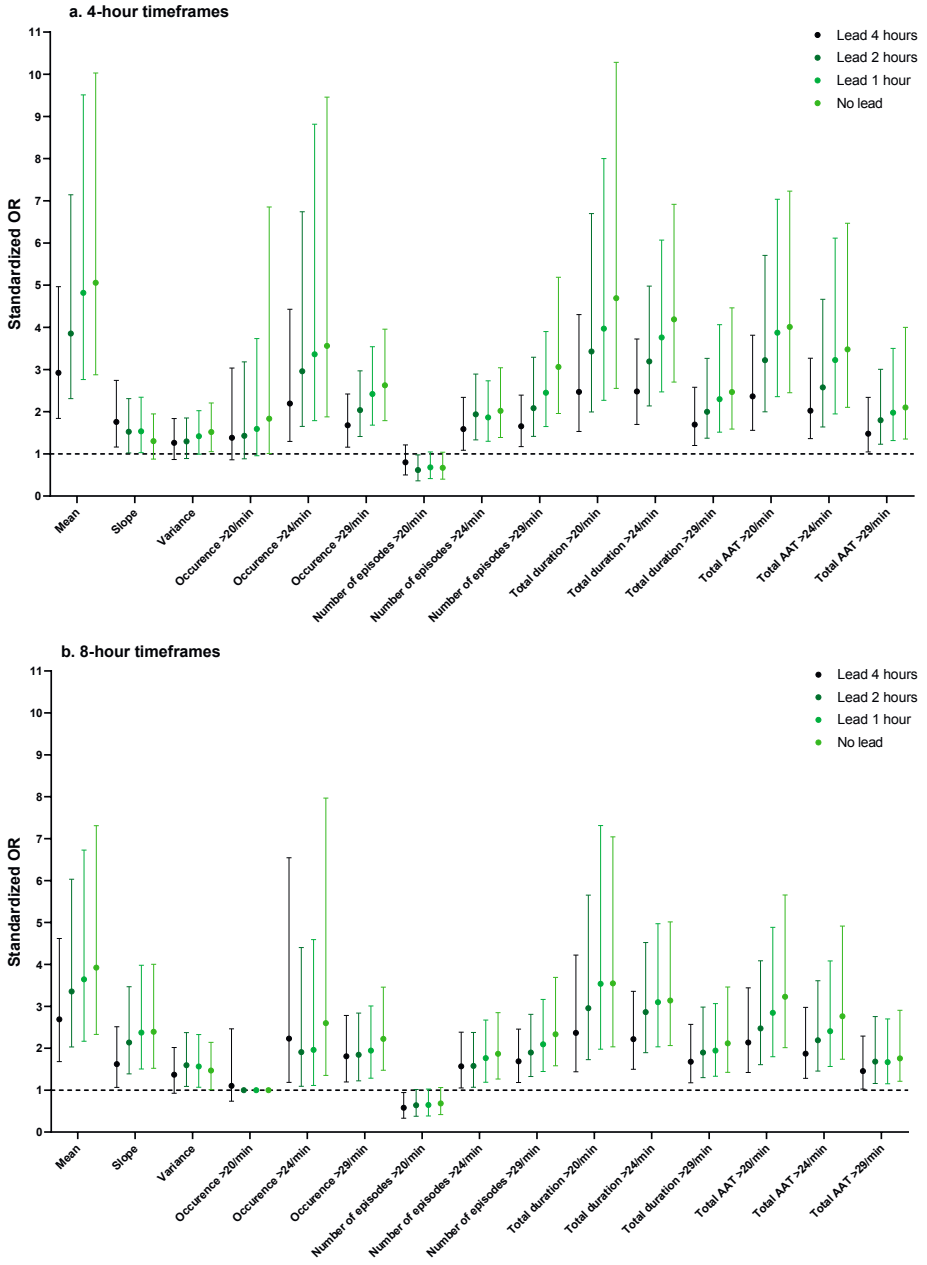


Figure 4. Standardised odds ratio's (OR) for respiratory rate.

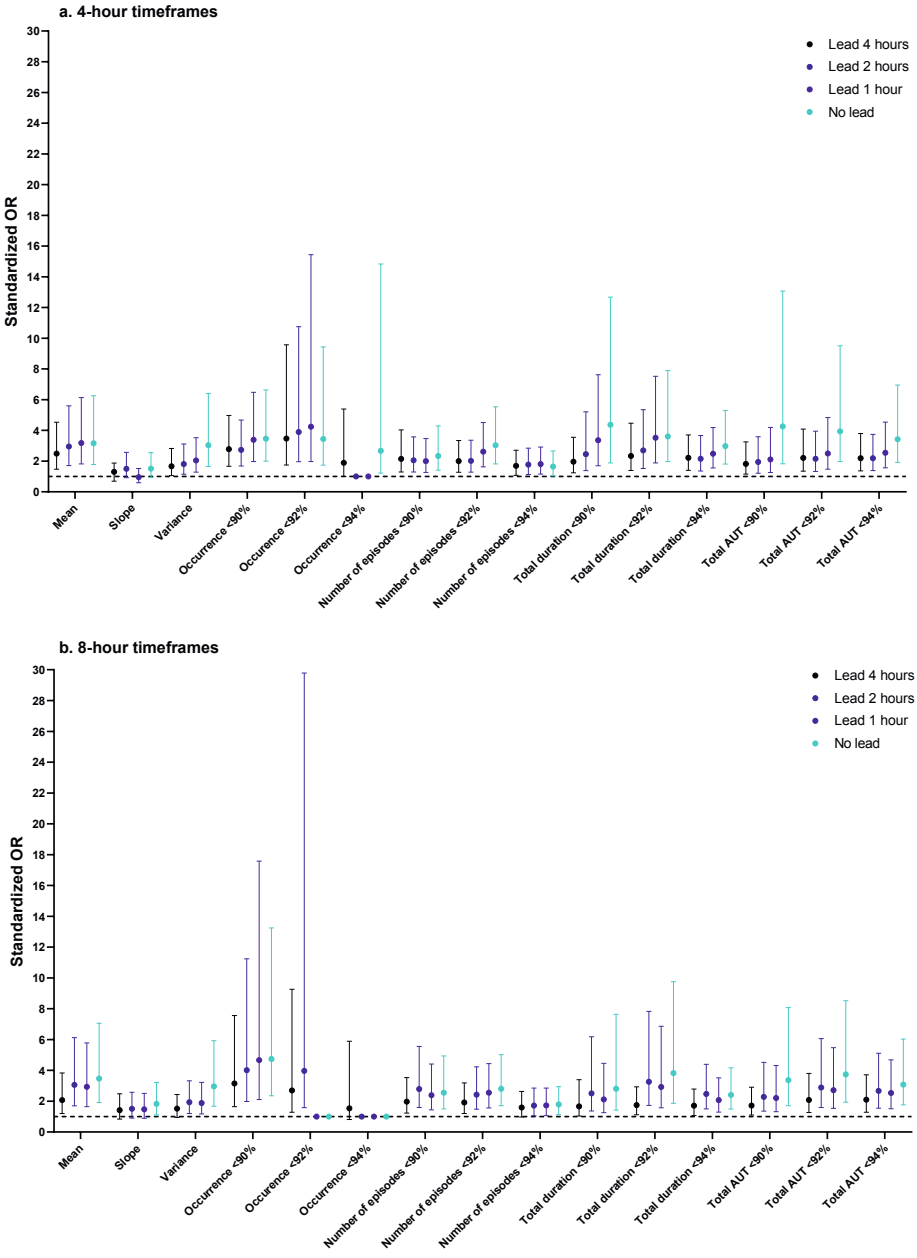


Figure 5. Standardised odds ratio's (OR) for oxygen saturation.

DISCUSSION

In this study, we aimed to explore which summary measures for continuously measured HR, RR, and SpO2 data could be helpful in recognising imminent respiratory insufficiency in COVID-19 patients at the general ward. We found that summary measures over timeframes of continuously measured data close to the endpoint of respiratory insufficiency showed stronger associations than timeframes further removed, and that 4-hour timeframes performed better than 8-hour timeframes. The summary measure 'mean' was consistently strongly associated with respiratory insufficiency for all vital parameters. The strength of associations of summary measures depended on the vital sign, timeframe and lead.

Comparison with Prior Work

RR has repeatedly been marked as the best discriminator to identify patients at risk for deterioration[19,20]. In our study we confirmed that RR showed stronger associations with respiratory insufficiency than HR. SpO2 was also strongly associated, which can partly be explained by the population (COVID-19 patients) and the endpoint (respiratory failure). In a previous study on trends in vital signs of hospitalised patients, Churpek et al.[8] used several summary measures for trend analysis of intermittent data to predict clinical deterioration. In Churpek's study the slope, mean and standard deviation were better predictors than the current value for HR and RR, and the mean performed well for SpO2. In our study, we confirmed a strong association of the mean of all three vital parameters with respiratory insufficiency. The slope and standard deviation however were less informative. This might be caused by differences between intermittently and continuously measured vital signs. Due to the high density of measurements, continuously monitored vital signs data show more variance than intermittent data in our experience, and is more subject to peaks and troughs depending on a patient's activity level. In the study of Akel et al.[9], the (intermittently measured) maximum RR and HR were also important predictors. We did not use the maximum value, since we expected the maximum value to rely highly on both activity level and outliers (e.g. due to coughing or talking), and would therefore not be clinically useful. A recent study did use summary measures for continuously measured vital signs, the mean, standard deviation, range, and mean absolute deviation, over 3-hour timeframes[21]. They created a machine learned model of these summary measures along with other data features, and managed to predict complications in postoperative patients with a lead of 12 hours. Unfortunately, this method does not allow for comparison of the value of these different summary measures. In our study, we only used leads up to 4 hours, to limit the number of computations. We found that shorter leads led to stronger associations. This might be an obvious finding, as vital instability often is a gradual process of decline, most pronounced

at the end when a patient becomes actually respiratory insufficient[22]. However, this finding nuances earlier failure-to-rescue statements and illustrates that the information content is less dens 12 hours prior to the event[23,24]. In current clinical practice (and at our study ward) the NEWS2 is often used to detect deterioration[13]. Our thresholds were based on this score. In the NEWS2, more severe threshold breaches receive more points, and thus correspond with a higher risk of poor outcome. In this line, we would have expected summary measures of more severe thresholds to have a stronger association with respiratory insufficiency. Interestingly, this was not the case.

Methodological Decisions and Limitations

In this exploratory study, we made several methodological decisions that affected the results. First of all, we chose a cross-sectional method to determine the association of summary models with respiratory insufficiency, by comparing patients who reached the endpoint with those who did not. A longitudinal assessment of risk for respiratory insufficiency (e.g. using a dynamic prediction model) might be an approach that is more in line with clinical practice. In a dynamic prediction model, previously recorded data of a patient can be included to update the estimated patient's risk of developing the outcome of interest at consecutive time points. However, the sample sizes of current continuous monitoring studies are relatively small and the populations heterogeneous, which may complicate the development of robust prediction models[10]. Larger studies and open sharing of continuous data might speed up the process of developing and validating such longitudinal dynamic models. A second methodological key decision was to only select summary measures, timeframes and models that could easily be understood by health care professionals. Hereby, we limit the 'black box' effect of complex models, of which the exact computational procedure is opaque[25]. These models might have better predictive accuracy, but are unintelligible for clinical professionals, which makes clinicians reluctant to use and rely on them[25]. For this explorative study, we aimed to increase the understanding of the association between continuous vital signs and deterioration, and therefore we chose a transparent methodology. Machine learning models however have proven to be more accurate than current practice in several fields of medicine[26]. In predicting deterioration, some studies have shown that machine learning models outperform 'simple' regression models[9,27,28]. A recent study has developed a machine learning model that uses several summary measures of vital signs to predict deterioration of high risk patients[21]. Explorative studies like our study could provide insight into which summary measures to include into such a machine learning model[21]. A final addition to a model with continuous monitoring data could be non-vital sign parameters, such as the amount of administered oxygen. The combination of administered oxygen with RR and SpO2 has previously shown to accurately predict respiratory insufficiency in COVID-19 patients[29]. Regardless of the type of prediction

model or algorithm that is constructed using continuously measured vital signs data, any model should be well calibrated and be externally validated before implementation in clinical practice[30].

Strengths and Limitations

Beside the above mentioned methodological considerations, this study has several limitations. We relied on a small convenience sample size which resulted in limited accuracy, and were unable to validate our findings in a larger dataset. A significant part of the initial sample had to be excluded for lack of continuous monitoring data within the needed 12-hour timeframe for multiple reasons, such as loss of connection with the patch, nurses that were not able to or forgot to connect a patient to the system, or patients who reached the endpoint before or within short time after getting the patch. The exact reasons for these periods of missing data are hard to reconstruct retrospectively. Additionally, there were differences in the number of patients with available data for each vital sign. Patients that were relatively less ill wore the pulse oximeter less often, because they found it annoying, they were mobilizing beyond the reach of the monitor, or the nurse agreed it was no longer necessary to monitor SpO2. The smaller sample size with relatively high percentage of patients reaching the endpoint might have strengthened the association between SpO2 and respiratory insufficiency. For control patients, we included the 24-36 hours of data following admission to the ward. This was a pragmatic decision, but the choice of timeframes early in the admission period could have influenced the results. Nevertheless, respiratory insufficiency also mostly occurred early in the admission, so the timing of the selected data of the control group and the respiratory insufficiency group were fairly similar. Conclusions can only be drawn for COVID-19 patients. For other patient populations, alternative vital signs and summary measures might be more informative[31]. Since the continuous monitoring system was not implemented alongside of standard intermittent monitoring, but instead of standard intermittent monitoring, we could not compare the performance of summary measures with care as usual. All continuous data was visible for nurses and physicians during the study. The vital sign aberrations they spotted during monitoring will have influenced their decision to start treatment, thus influencing the endpoint. However, staff was limited in the options for additional treatment, and thereby also limited in their influence to avoid the endpoint. Moreover, we do believe the decision to start 15L/min oxygen therapy, high flow oxygen therapy or mechanical ventilation was certainly not solely based on the continuous data but mostly on the overall clinical condition of the patient. Due to the retrospective nature of the study, we relied on documentation in the electronic patient record to determine the time point of respiratory insufficiency. A prospective design might result in a more accurate estimation of the timing of onset.

Considerations for Future Research

Summary measures of vital signs that show a strong association with the occurrence of respiratory insufficiency could be helpful in several ways. First of all, they might be used in a clinical score for direct use by nurses and physicians. For intermittently measured vital signs, the early warning score created both a framework to measure vital stability, and a language for nurses to communicate instability to a physician[32]. Nurses are empowered by these aspects of the early warning score. Furthermore, they can use the early warning score to easily package and summarise information about a patient, which helps physicians to prioritise care[32]. For continuous data, no such language or score currently exists to communicate observations of continuously measured vital signs. Summary measures could be used to create one. For example, the most associated summary measures could be used to create an easy to use prognostic score, or could directly aid nurses in physicians to interpret, summarise, and articulate continuous monitoring data of COVID-19 patients.

Secondly, summary measures may be useful to be incorporated in an automatic alarm system. Especially under circumstances where the nurse-to-patient ratio is low, e.g. during night shift, an alarm system with high predictive accuracy that could detect deteriorating patients that otherwise might have been missed, would be valuable[33]. Clinical scores however might not be suitable for automatic alarming. Early warning scores have previously been applied as an alarm system, by using the means of continuously monitored vital signs over a short period (e.g. 5 minutes) as input values[34,35]. The downside of this strategy is that some thresholds of commonly used early warning score, e.g. RR >20/min or HR >90/min in the NEWS2, are easily breached, especially in active patients. In our study, the mean RR for patients who did not experience respiratory insufficiency was 20.5/min, thus half of all measurements would score a point on the NEWS2. In a recent study, both patient who did and did not experience deterioration met criteria for a high early warning score if continuous monitoring of vital signs was used[35]. This high number of threshold breaches could, if followed up with an alarm, lead to alarm fatigue[36]. To develop an adequate alarm system, a new predictive model for continuous monitoring data might be more helpful, in which summary measures could be used as input values instead of single threshold breaches. Since such an alarm system can operate on the background and does not have to be used by hospital professionals directly, it allows for more complexity than the clinical score that is used on the ward. The previously mentioned study by Kristinsson et al.[21] is a promising example.

CONCLUSION

We explored several possible ways to summarise continuous vital signs data of COVID-19 patients on the general ward. The mean showed a relatively strong association with respiratory insufficiency for HR, RR and SpO2. Overall, shorter timeframes with smaller leads showed stronger associations. Highly associated summary measures and combinations could be used in a clinical prediction score or algorithm for an automatic alarm system.

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SUPPLEMENTAL MATERIAL

Supplemental table 1. Considered and selected summary measures.

Summary measure	Threshold related	Selected for analysis
Mean	No	Yes
Standard deviation	No	No
Variance	No	Yes
Slope	No	Yes
Occurrence of episode	Yes	Yes
Number of episodes	Yes	Yes
Total duration of episodes	Yes	Yes
Maximum duration of episode	Yes	No
Mean duration of episode	Yes	No
Total area above/under threshold	Yes	Yes
Maximum area above/under threshold	Yes	No
Mean area above/under threshold	Yes	No

Supplemental table 2. Baseline characteristics of patients stratified by availability of vital sign.

	All / heart rate (n=334)	Respiratory rate (n=288)	Oxygen saturation (n=238)
Age (median, IQR)	65 (55.3-73.8)	65 (56-73.3)	65 (56-74)
Male sex (n, %)	207 (62.0%)	186 (64.5%)	144 (60.5%)
Charlson Comorbidity Index (median, IQR)	0 (0-1)	0 (0-1)	0 (0-1)
Dexamethasone during admission (n, %)	262 (78.4%)	224 (77.8%)	198 (83.2%)
Diagnosed with pulmonary embolism (n, %)	23 (6.9%)	18 (6.3%)	20 (8.4%)
Treatment restrictions[a] (n, %)	91 (27.2%)	74 (25.7%)	65 (27.3%)
Length of hospital stay (median, IQR)	7 (5-12)	7 (5-12)	8 (5-13)
ICU or MCU admission (n, %)	57 (17.1%)	52 (18.0%)	38 (16.0%)
- Included in 'resp insuf' group[b]	27 (8.1%)	25 (8.7%)	22 (9.2%)
Mortality (n, %)	23 (6.9%)	19 (6.6%)	17 (7.1%)
Endpoint: respiratory insufficiency (n, %)	66 (19.7%)	57 (19.8%)	54 (22.7%)

IQR: inter quartile range, ICU: intensive care unit, MCU: medium care unit, resp insuf: combined endpoint of respiratory insufficiency.

[a]Treatment restrictions: no resuscitation, no ventilation, and/or no ICU admission.

[b]If a patient was monitored after ICU admission and did not reach the endpoint while being monitored, he/she was not included in the 'respiratory insufficiency' group.

Supplemental table 3a. Mean of summary measures 4-hour timeframes.

Parameter	Threshold	Summary measure	Total	No resp insuf.	Resp. insuf.
Heartrate	None	Mean (/min)	74.4	71.7	86.1
		Slope (/min/hour)	0.04	-0.17	0.99
		Variance (/min^2)	53.6	52.8	56.7
	>90/min	Occurrence	0.54	0.48	0.75
		Number of episodes	2.47	2.19	3.66
		Total duration (min)	37.5	27.2	81.6
		Total area above threshold	907.2	547.9	2450.9
	>110/min	Occurrence	0.19	0.16	0.35
		Number of episodes	0.67	0.49	1.45
		Total duration (min)	7.46	4.24	21.3
		Total area above threshold	187.3	89.9	605.7
	>130/min	Occurrence	0.037	0.02	0.12
		Number of episodes	0.096	0.035	0.36
		Total duration (min)	2.00	0.98	6.40
		Total area above threshold	36.2	22.5	94.9
Respiratory rate	None	Mean (/min)	21.5	20.5	25.6
		Slope (/min/hour)	-0.04	-0.12	0.30
		Variance (/min^2)	5.46	5.10	6.94
	>20/min	Occurrence	0.89	0.88	0.97
		Number of episodes	4.15	4.37	3.23
		Total duration (min)	124.9	107.5	196.5
		Total area above threshold	622.0	440.9	1368.0
	>24/min	Occurrence	0.65	0.58	0.93
		Number of episodes	3.27	2.75	5.42
		Total duration (min)	52.4	33.4	130.9
		Total area above threshold	229.2	125.5	656.2
	>29/min	Occurrence	0.25	0.18	0.56
		Number of episodes	0.98	0.55	2.77
		Total duration (min)	13.2	5.88	43.3
		Total area above threshold	56.1	25.14	183.5
Oxygen saturation	None	Mean (%)	94.8	95.2	93.3
		Slope (%/hour)	-0.079	-0.030	-0.26
		Variance (%^2)	5.28	4.47	8.19
	<94%	Occurrence	0.81	0.77	0.98

Supplemental table 3a. (Continued)

Parameter	Threshold	Summary measure	Total	No resp insuf.	Resp. insuf.
		Number of episodes	5.89	5.24	8.23
		Total duration (min)	60.9	47.7	108.8
		Total area under threshold	215.7	159.0	421.6
	<92%	Occurrence	0.60	0.51	0.93
		Number of episodes	3.12	2.37	5.84
		Total duration (min)	24.5	16.1	55.0
		Total area under threshold	95.4	63.9	210.0
	<90%	Occurrence	0.40	0.29	0.79
		Number of episodes	1.59	1.16	3.12
		Total duration (min)	10.2	6.16	24.9
		Total area under threshold	41.1	25.7	97.2

Resp. insuf.: reached the combined endpoint of respiratory insufficiency.

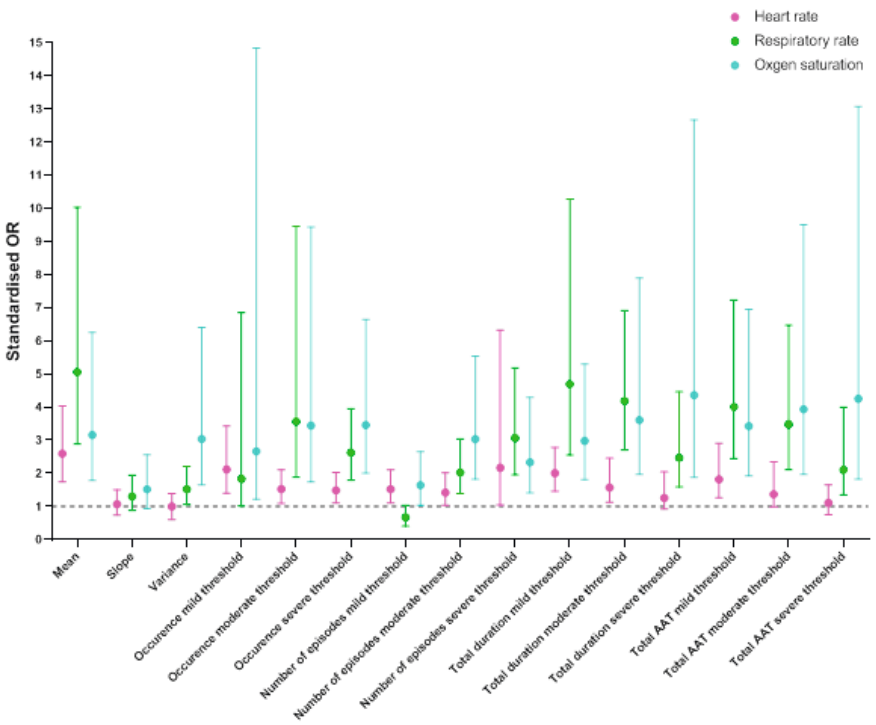
Supplemental table 3b. Mean of summary measures 8-hour timeframes.

Parameter	Threshold	Summary measure	Total	No resp insuf.	Resp. insuf.
Heartrate	None	Mean (/min)	75.0	72.9	84.5
		Slope (/min/hour)	-0.35	-0.59	0.74
		Variance (/min^2)	71.6	70.8	75.6
	>90/min	Occurrence	0.67	0.64	0.80
		Number of episodes	5.48	5.18	6.84
		Total duration (min)	73.8	58.1	145.8
		Total area above threshold	1574	1058	3946
	>110/min	Occurrence	0.27	0.24	0.41
		Number of episodes	1.20	0.96	2.33
		Total duration (min)	13.22	8.00	37.2
		Total area above threshold	271.2	138.1	882.1
	>130/min	Occurrence	0.050	0.028	0.15
		Number of episodes	0.14	0.062	0.48
		Total duration (min)	2.92	1.34	10.2
		Total area above threshold	41.5	25.5	115.0
Respiratory rate	None	Mean (/min)	21.6	20.9	25.1
		Slope (/min/hour)	-0.095	-0.17	0.24
		Variance (/min^2)	7.11	6.65	9.20
	>20/min	Occurrence	0.96	0.96	0.99

Supplemental table 3b. (Continued)

Parameter	Threshold	Summary measure	Total	No resp insuf.	Resp. insuf.
		Number of episodes	8.47	8.91	6.46
		Total duration (min)	258.3	231.3	380.7
		Total area above threshold	1254.4	986.4	2470
	>24/min	Occurrence	0.78	0.74	0.95
		Number of episodes	7.00	6.27	10.3
		Total duration (min)	107.4	79.1	235.6
		Total area above threshold	444.7	291.2	1141
	>29/min	Occurrence	0.35	0.29	0.63
		Number of episodes	2.06	1.37	5.17
		Total duration (min)	24.7	14.0	73.2
		Total area above threshold	96.6	54.1	289.3
Oxygen saturation	None	Mean (%)	95.0	95.3	93.6
		Slope (%/hour)	-0.046	-0.013	-0.17
		Variance (%^2)	5.78	5.14	8.30
	<94%	Occurrence	0.89	0.86	0.99
		Number of episodes	11.2	10.0	15.6
		Total duration (min)	124.2	99.4	220.3
		Total area under threshold	378.4	288.9	726.2
	<92%	Occurrence	0.71	0.65	0.98
		Number of episodes	5.72	4.45	10.7
		Total duration (min)	49.4	33.1	112.5
		Total area under threshold	162.7	115.9	344.2
	<90%	Occurrence	0.42	0.52	0.93
		Number of episodes	2.08	2.79	5.54
		Total duration (min)	13.43	20.1	46.1
		Total area under threshold	47.3	67.9	148.0

Resp. insuf.: reached the combined endpoint of respiratory insufficiency.



Supplemental figure 1. Standardised odds ratios of summary measures for heart rate, respiratory rate and oxygen saturation over a timeframe of 4 hours without a lead OR: odds ratio, AAT: area above threshold, AUT: area under threshold.

PART II

The implementation of continuous monitoring

CHAPTER 4

Interpretation of continuously measured vital signs data of COVID-19 patients by nurses and physicians at the general ward: a mixed methods study

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ABSTRACT

Background – Continuous monitoring of vital signs is introduced at general hospital wards to detect patient deterioration. Interpretation and response currently rely on experience and expert opinion. This study aims to determine whether consensus exist among hospital professionals regarding the interpretation of vital signs of COVID-19 patients. In addition, we assessed the ability to recognise respiratory insufficiency and evaluated the interpretation process.

Methods – We performed a mixed methods study including 24 hospital professionals (6 nurses, 6 junior physicians, 6 internal medicine specialists, 6 ICU nurses). Each participant was presented with 20 cases of COVID-19 patients, including 4 or 8 hours of continuously measured vital signs data. Participants estimated the patient's situation ('improving', 'stable', or 'deteriorating') and the possibility of developing respiratory insufficiency. Subsequently, a semi-structured interview was held focussing on the interpretation process. Consensus was assessed using Krippendorff's alpha. For the estimation of respiratory insufficiency, we calculated the mean positive/negative predictive value. Interviews were analysed using inductive thematic analysis.

Results – We found no consensus regarding the patient's situation (α 0.41, 95%CI 0.29-0.52). The mean positive predictive value for respiratory insufficiency was high (0.91, 95%CI 0.86-0.97), but the negative predictive value was 0.66 (95%CI 0.44-0.88). In the interviews, two themes regarding the interpretation process emerged. "Interpretation of deviations" included the strategies participants use to determine stability, focused on finding deviations in data. "Inability to see the patient" entailed the need of hospital professionals to perform a patient evaluation when estimating a patient's situation.

Conclusion – The interpretation of continuously measured vital signs by hospital professionals, and recognition of respiratory insufficiency using these data, is variable, which might be the result of different interpretation strategies, uncertainty regarding deviations, and not being able to see the patient. Protocols and training could help to uniform interpretation, but decision support systems might be necessary to find signs of deterioration that might otherwise go unnoticed.

INTRODUCTION

Continuous wireless monitoring of vital signs is introduced at general hospital wards for it's potential to observe vital (in)stability in time and remote[1]. During the COVID-19 pandemic, continuous monitoring gained even more interest since hospitals had to deal with a high number of severely ill patients who were cared for in isolation units. Although a recent observational study showed a reduction in intensive care unit (ICU) admissions after introduction of continuous monitoring[2], few randomised trials have been performed, and systematic reviews failed to show an unequivocal positive effect on patient outcomes[1,3]. Continuous monitoring is a multifactorial intervention that includes multiple technical, organisational and behavioural challenges. Many of the non-technical issues are scarcely researched and might benefit from a more structured approach to implementation. One of the important factors of implementation is training of hospital staff[4,5]. Previous studies show that nurses perceived an increased benefit of continuous monitoring if they were trained and confident in its use[6,7]. In addition, hospital professionals experience a learning curve over time as they grow more acquainted with the system[5]. Still, many nurses feel like they have insufficient knowledge to interpret vital signs trends, and are unsure which deviations are important to recognise[5]. No guidelines or clinical scores (such as the Early Warning Score for intermittently measured vital signs data) currently exist to assist in the interpretation of continuously monitored vital signs data at the general ward. Practice therefore relies on experience and expert opinion.

In this study we aimed to gain understanding of how nurses and physicians, with and without training and experience, handle continuously measured vital signs of COVID-19 patients. The main objective was to determine whether consensus exists among nurses and physicians on a patient's vital status, based on interpretation of continuously measured vital sign trends. Secondly, we assessed the ability of nurses and physicians to recognise which COVID-19 patients are becoming respiratory insufficient, using the continuous monitoring data. Lastly, we aimed to identify how the interpretation process of hospital professionals works, and identify aspects of interpretation that should be included in training.

METHODS

We performed a mixed methods study at the tertiary medical centre University Medical Centre Utrecht, The Netherlands, between April 6th and August 9th 2022. At the designated COVID-19 ward of the hospital a continuous monitoring system had been in place between

April 2020 until March 2021, but no continuous monitoring system was in place during the study period. Participation consisted of two parts: a case review of 20 cases of COVID-19 patients, followed by a semi-structured interview. Ethical review was waived by the local Medical Ethics Review Committee (MERC Utrecht 22-091).

Participant inclusion

Three groups of hospital professionals from the internal medicine department (general ward nurses, junior physicians, medical specialists) were included to participate in the study. A fourth group consisting of ICU nurses was added to function as a comparison group, since ICU nurses are trained and experienced in continuously measuring vital signs. Participants were eligible if they had gained experience with COVID-19 patients care in the previous two years. Participants were recruited via a notice in the weekly newsletter, or they were approached by the research team directly. The research team aimed to include a selection of participants representative of the hospital staff with regard to baseline characteristics. Participants were asked for informed consent digitally and the following baseline information was collected: age, gender, function, years of clinical experience, and previous experience with continuous monitoring.

Case review questionnaire

The case review consisted of 20 real-life cases that were included in a previously published study on continuous monitoring of COVID-19 patients (MERC UMC Utrecht, 20-365)[8]. Cases were randomly selected from a prospective cohort with 429 patients depending on the outcome variable "respiratory insufficiency". Ten cases (50%) were randomly selected from the cohort that developed respiratory insufficiency, the other ten cases from the cohort that did not develop respiratory insufficiency. Participants were unaware of this fifty-fifty case mix. Per outcome category, continuous data was alternately plotted over 4- and 8-hour time series. For patients who developed respiratory insufficiency, the time series ended within 2 hours before the occurrence of this endpoint. Respiratory insufficiency was defined as the need for 15L/min or more oxygen administration, mechanical ventilation, resuscitation or death, whichever came first. Cases were presented anonymously. For each case, a short summary including age, sex, relevant medical history, duration of hospitalization and list of relevant medications was given. Subsequently, four visual plots of continuously monitored data were shown: heart rate, respiratory rate, oxygen saturation and amount of administered oxygen. Per case, the participants had to answer four questions: 1. Do you consider the situation of the patient improving, stable or deteriorating? 2. Would you take action in this situation? 3. Do you expect this patient to become respiratory insufficient in the next few hours? 4. Would you score this case easy or difficult to interpret? The case review questionnaire was sent digitally to the participant within one day before the scheduled interview, using

the data capture tool Castor version 2022.1 (Castor Electronic Data Capture (2022)). The questionnaire took approximately 30 minutes to finish.

Semi-structured interview

The focus of the qualitative part of the study was to understand the underlying rationale for the answers participants had given during the case review. We aimed to understand how the interpretation process works and unravel aspects of continuously measured vital signs that influence interpretation. The semi-structured interview guide can be found in supplemental material 1. Interviews were held one on one, either in real life or via the video call using Microsoft Teams. The completed questionnaires of the participant was shown to refer to during the interview. The interviewer (HvG) had no previous experience with or training in scientific interviewing. She was coached and guided by experienced interviewers in the research group (LS, KvL, MB) throughout the study. The interviewer was employed as PhD student during the study and participants knew her as a PhD student with focus on continuous monitoring of vital signs. In the study information it was stated that the interviewer wanted to 'gain insight into the decision making process'. Both the questionnaire and interview were pilot tested before the start of the study. During interviews, audio was recorded for transcription. No field notes were made. Transcripts were not returned to participants for comments.

Sample size and quantitative analysis

The sample size was determined based on the first research question: Is there consensus amongst nurses and physicians over a patient's vital status based on continuously measured data? To determine the interobserver agreement we used Krippendorff's alpha coefficient, since this estimate allows for more than two answer options and more than two observers[9]. We aimed to determine the interobserver agreement for the entire sample and for the four hospital staff groups individually. Based on equal a-priori probability of the three outcome options (improving, stable, deteriorating) and a Krippendorff's alpha of at least 0.8 for sufficient agreement, and 0.67 for moderate agreement, 116 values were needed per group[10]. By using 20 cases per participant and 6 participants per group, we acquired 120 values per group. The confidence interval (CI) was calculated using a bootstrapping method with 2000 iterations. Secondly, we determined the interobserver agreement for 'action' and 'expected respiratory insufficiency'. For the second research question, we determined the positive and negative predictive value of the estimation of pending respiratory insufficiency by hospital staff per participant, and used these to calculate the mean positive and negative predictive value. A 95%CI was used for hypothesis testing. R software version 4.0.3 (R foundation for Statistical Computing (2021)) was used for quantitative analysis.

Qualitative analysis

All interviews were transcribed using a naturalized verbatim style by HvG[11] and uploaded in data analysis software NVivo 12 (QRS International Pty Ltd. (2018)). Subsequently, we used inductive thematic content analysis strategy to find recurrent themes within the interviews[12]. The first two stages (familiarizing with data, generating the initial codes, and searching for themes) were performed by HvG and MJMB separately. Reviewing, defining and naming themes, and producing reports was done by HvG and MJMB together, and was hereafter discussed with LS. The study reported following the consolidated criteria for reporting qualitative research (COREQ) guidelines[13].

Mixing methods

The quantitative and qualitative data were mixed in two ways. First of all, the qualitative part of the study (the interview) built on the quantitative questionnaire, and the answers to the questionnaire were used in the interview. Secondly, the results of the quantitative and qualitative part were merged in the discussion[14].

RESULTS

Of the 24 participants, 5 contacted the research team after the notice in the newsletter, and 19 were approached personally (table 1). All participants had worked multiple shifts at COVID-19 units in the previous 2 years. All included nurses were female, whereas only 1 of the 6 medical specialists was female. Junior physicians had the least clinical experience (median of 2 years, range 1-4), medical specialists had the most experience (median 17.5 years, range 8-18). All ICU nurses had experience with continuous monitoring during their daily work at the ICU. One medical specialist had experience with the continuous monitoring at the COVID-19 unit between 2020-2021, and one junior physician had assisted in another study on the use of a wearable sensor for continuous vital signs monitoring. The other participants had little or no experience with continuous monitoring outside the high care unit.

Quantitative analysis

No agreement on the situation of the patient (improving, stable or deterioration) was found among hospital professionals, both in the overall analysis and the subgroup analyses (table 2, supplemental table 1). No agreement was found on whether to take action. Agreement was not found on the expectation of respiratory insufficiency, but could also not be ruled out, with an upper limit of the 95%CI in the 'moderate agreement' range. For the prediction of respiratory insufficiency, the mean positive predictive value of all participants was 0.91 (95%CI 0.86-0.97). The mean negative predictive value was 0.66 (95%CI 0.44-0.88).

Table 1. Participant characteristics.

	All (N=24)	Nurses (N=6)	Junior physicians (N=6)	Medical specialists (N=6)	ICU nurses (N=6)
Age (median, range)	31 (23-56)	25 (22-29)	28 (25-31)	42.5 (35-45)	31.5 (30-56)
Gender (N)					
- Female	14	6	3	1	4
- Male	10	0	3	5	2
Recruitment (N)					
- Newsletter	5	2	0	0	3
- Personally approached	19	4	6	6	3
Years of clinical experience (median, range)	5.5 (1-28)	3.75 (2.5-6)	2 (1-4)	17.5 (8-18)	10.5 (5-28)
Experience with continuous monitoring (N)					
- Previous experience	8	0	1	1	6
- Little or no experience	16	6	5	5	0

Table 2. Analysis of interrater agreement using Krippendorff's alpha coefficient (α). Grades of agreement of α: <0.67 low agreement, 0.67-0.80 moderate agreement, >0.80 high agreement.

	All	Nurses	Junior physicians	Medical specialists	ICU nurses
Situation (α, 95%CI)	0.41 (0.29-0.52)	0.32 (0.198-0.45)	0.46 (0.35-0.57)	0.49 (0.37-0.60)	0.44 (0.33-0.54)
Action (α, 95%CI)	0.37 (0.20-0.54)	0.32 (0.12-0.50)	0.36 (0.16-0.54)	0.43 (0.23-0.62)	0.52 (0.34-0.68)
Respiratory insufficiency (α, 95%CI)	0.59 (0.40-0.76)	0.59 (0.41-0.76)	0.65 (0.47-0.82)	0.71 (0.52-0.87)	0.52 (0.36-0.70)

Qualitative analysis

We performed an inductive analysis to find recurrent themes on how continuously measured vital signs at was interpreted by hospital professionals. Two main themes emerged: 'Interpretation of deviations' and 'Inability to see the patient'.

Interpretation of deviations

When assessing the vital sign data, participants where often focussed on finding deviations. Since the cases were all COVID-19 patients, deviations in respiratory rate and oxygen

saturation received the most attention. Participants used one of three strategies to find these deviations: by assessing thresholds breaches (e.g. a respiratory rate above 30/min), by assessing trends (an increasing respiratory rate over time), or, most often, by using both thresholds and trends (a respiratory rate that increased over time and exceeds 30/min). If no deviations were found, participants stopped the assessment, and the patient was deemed stable. These cases were usually considered easy. If deviations where constantly present and very clearly pointing in one direction, e.g., an oxygen saturation that progressively decreased over the entire plot from 98% to 88%, participants considered the case easy too. Very short deviations were often disregarded by participants as being measurement errors or motion artefacts. However, most participants experienced difficulty if deviations occurred irregularly. Participants felt uncertain how long or severe a deviation had to be to reflect true patient deterioration. Similarly, participants did not know how many hours of data were needed for a valid estimation of the patient's situation. Consequently, lack of knowledge of target values, periods of missing data, and fluctuating trends posed difficulties for participants. One participant said: "*..and for example the first 2 hours is stable, but the next 2 hours has fluctuations and after that it is stable again. Are you going to intervene, or accept it, or how should you interpret this*". In these cases, participants tried to find more information or conformation in other sources, such as corresponding deviations in other vital signs, information on the time of day, or patient history. For example, obstructive sleep apnoea disease could be a logical explanation for nightly dips in oxygen saturation. If a satisfying explanation could be found here, participants were more confident to make a decision regarding the patient's status: "*It's likely that, there is an increased respiratory rate here, an increased heart rate, maybe she was doing personal care, or she went to the toilet. I see it's 9 o'clock in the evening, she was probably doing something*". In cases when interpretation was considered difficult, participants often fell back on using the last vital sign values of the plot and comparing these against thresholds, since this is the method they currently use on intermittent vital signs: "*..you try to look at the trend, but you end up interpreting everything as a snapshot. As you are used to, that there is one measuring moment*". Many participants did experience a learning curve during the study, gaining more confidence interpreting deviations after they had seen more cases. This learning curve was experienced by all hospital professionals, including ICU nurses. ICU nurses indicated that they were not used to looking at vital signs data this way either, and mostly rely on threshold alarms. They did indicate to use repeated threshold alarms as an alternative form of trend monitoring: the increase or decrease of a threshold alarm could be seen as a trend.

Inability to see a patient

Of the presented context information, only the amount of oxygen therapy was used regularly, to determine the risk of a patient becoming respiratory insufficient. The remaining patient characteristics, such as age, gender, medication, and comorbidity,

were often read, but seldom used. Participants indicated that what they really needed, instead of these patient characteristics, was a live patient evaluation. Especially in cases of possible patient deterioration, participants missed the possibility to examine the patient. To physically see the patient, and to hear what symptoms they experience, could help provide context to findings in the vital signs data: "*If I would see these [plots], I would first go to the patient to see how he is doing, what do I observe, and then verify, does that match with what the values tell me*". Participants often tried to make an estimation of possible exhaustion of the patient, which was hard to determine based on vital sign values alone. Especially for patients with an 'unstable' starting situation, e.g., a lot of oxygen therapy, participants had trouble to determine whether a patient was near the edge of exhaustion. In contrast, two participants said to have little difficulty interpreting the data without seeing the patient. One of them said: "*I am surprised by with how much, how little, data you can still have an idea [of the patient's situation]*".

DISCUSSION

In this study, we aimed to gain understanding of how nurses and physicians currently handle continuously measured vital signs data of COVID-19 patients, presented graphically as trend plots. We found little agreement among hospital professionals on the interpretation of stability of a patient's situation and inconsistent ability to recognise respiratory insufficiency, which might be the result of variable interpretation strategies, uncertainty regarding deviations in continuously measured vital signs data, or not being able to see the patient.

The variability and uncertainty in interpretation by participants might be one of the underlying reasons for the lack of consensus regarding a patient's vital stability. Hospital professionals usually try to quantify findings in vital signs to be able to communicate them with other hospital professionals, prioritize workload, and make decisions regarding escalation of care[15,16]. In this study, hospital professionals struggled to quantify findings of continuously measured data. They were most confident in pointing out threshold breaches, which they are used to when using intermitted monitoring, but struggled to quantify the time related aspect of continuously measured such as length and frequency. This might be due to the lack of knowledge or experience, but could also be because this process occurs more subconsciously. Hospital professionals do register changes over time, but do not yet have the quantifying language to express these findings. In a previous study on continuous monitoring, nurses indicated to use continuous monitoring to "*..make sure that, just from a glance, that nothing has changed*"[16]. Without guidelines about when the length or frequency of a deviation starts to be concerning, the estimation of patient stability based on continuously measured data is bound to be a grey area.

The observed lack of consensus regarding patient stability might complicate the collaboration between hospital professionals, a collaboration which is important for successful execution of a rapid response to deterioration. Therefore, more information is needed on which deviations are indicators of deterioration. This includes not only the height or depth of the deviation, but also the length, frequency, and context. A clinical decision support protocol on how to quantify continuously measured vital signs data, and what action should be taken if deviations are found, could uniform the interpretation by hospital professionals and empower them to communicate patient deterioration based on continuously measured vital signs.

The results of this study underline the difficulty to interpret continuously monitored vital signs data, while not being able to see the patient. Seeing and speaking to a patient is indisputably an important part of patient evaluation to collect information on signs and symptoms[17,18]. Furthermore, a patient's symptoms can trigger the non-analytical thought process that results in a 'gut feeling', which is a valuable part of the decision making process of nurses and physicians[18–20]. Although some decisions could be made based on vital signs data alone, physical evaluation was most commonly mentioned as missing in our study by both nurses and physicians. When taking intermittent vital signs, patient observation usually precedes vital sign evaluation. Physical cues are often early signs of deterioration, and vital signs are then used to confirm or quantify these findings[18,21,22]. With continuous monitoring, this can be done similarly, by evaluating the patient first and then comparing findings with the vital signs data of the past hours. However, while vital signs data are now continuously available, physical examination is not. We therefore might have to reverse the order and use clues in vital signs to find those patients who need bedside examination.

Not being able to do a physical examination of the patient might be a challenge especially for interventions including a remote monitoring centre[23]. In these centres, staff (often nurses) are appointed to monitor patients remotely and alert the nurses and physicians at the ward if needed. For these professionals, knowledge of trend interpretation without patient assessment is of the utmost importance. However, a remote monitoring strategy that solely relies on vital signs data will not be maximally effective. Therefore, remote monitoring centres have found solutions to create a more complete remote patient evaluation. Virtual ways of assessing the patient have been introduced, including two-way video and audio connection, and the remote monitoring centre is included in the multidisciplinary care for patients to have access to more context information[23].

Previous studies into learning trajectories of continuous monitoring described a learning curve to work with a new method to monitoring vital signs[5,24]. Jones et al.[24] described

five stages of a learning trajectory for (wired) telemonitoring, supervised by cardiac care unit (CCU) nurses. The first three stages involve technical training in the use of the monitoring system, similar to what current projects starting with continuous remote monitoring experience. During these stages, the hospital staff needs to gain confidence in the reliability of measurements. Currently, the trust in the validity of continuously measured data is lower than in the validity of intermittently measured vital signs data[16]. In our study too, the possibility of 'measurement errors' was often mentioned by participants. The last two stages of the described learning trajectory involve gaining knowledge about interpretation, which takes several education days, e-learnings, and learning on the job. The role of CCU staff is critical in this strategy, since they are the experts providing education, and are partly responsible for the monitoring of patients. When introducing continuous remote monitoring at the general ward, there is a clear need for such experts, who know how to interpret data and are confident to teach others. We assumed that ICU nurses, who work with continuous vital signs data on a daily basis, would be experts in interpreting trend data. However, the ICU nurses in our study indicated that looking at graphical trends of vital signs was new to them, and they usually focused more on alarm thresholds instead of trends. Consciously using trends of vital signs appears to be a very specific way of looking at data that is not commonly practiced at the ward, and therefore finding suitable experts and teachers might prove challenging.

Even though there is a wish to recognise deterioration earlier, vital sign abnormalities have to be obvious before hospital staff feel the need to intervene[25]. In this study, participants indicated that respiratory insufficiency is easily recognised when abnormalities are severe, but not if they are moderate or fluctuating. They were seldom wrong when indicating that a patient was becoming respiratory insufficient, but missed some cases that were less obvious. Nurses indicate that alarms are not needed when continuous data is regularly assessed[26] and might even lead to alarm fatigue[27]. However, alarms might be necessary to detect signs of deterioration that are currently missed by hospital professionals, provide decision support in case of moderate or uncertain deviations, or help to find those patients that need clinical assessment. We should aim to find an alarm strategy that provides useful decision support without rendering too many false alarms. For future research, it would be interesting to see if these cases are more easily recognised if hospital staff has more training and experience with continuous monitoring, and when real life patient assessment is readily available.

Strengths and limitations

This study not only investigated to what extent the interpretation of vital signs is similar among hospital professionals, but also evaluated how this interpretation comes to be, and highlighted the difficulties that are encountered during interpretation. The study

was based on real, unfiltered data to create the most realistic situation. Because of the heterogeneous case pool, the emphasis was on the continuously measured vital signs data instead of the underlying disease. Nonetheless, since the interpretation process is influenced by the admission diagnosis, findings are most applicable to COVID-19 cases. Although we tried to make the interpretation process as realistic as possible, the study was still limited by the artificial circumstances of estimating a patient's condition with only paper-based information. However, these circumstances do resemble the situation for remote monitoring by personnel that has no direct access to the patient themselves. Because the cases were randomly selected, some cases of patients that experienced respiratory insufficiency yielded only very non-specific deviations, making it hard for hospital professionals to detect upcoming deterioration. It is not certain that a technological solution would have been able to detect deterioration in these cases either. The participants included in the study were all enthusiastic to participate in a study regarding continuous monitoring, which might have led to selection bias. Although the subgroups differed in baseline regarding age, sex, and years of clinical experience, they did reflect the working population in our hospital. We incorrectly assumed that ICU nurses would be used to assessing trend data. Other groups of professionals, such as ICU physicians or anaesthetists, might be more used to this specific way of handling vital signs data and might therefore have been a more suitable comparison group.

CONCLUSION

Little agreement was found among hospital professionals regarding the estimation of patient stability based on continuously measured vital signs of COVID-19 patients. Differences might be the result of variable interpretation strategies, uncertainty regarding deviations in continuous monitoring data, and not being able to see the patient. Protocols and targeted training could help to unify the interpretation of continuously measured vital signs by hospital professionals. Decision support systems however might be necessary to detect cases of deterioration that are not easily recognised.

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SUPPLEMENTAL MATERIAL

Supplemental material 1. Semi structured interview guide (translated from Dutch).

- You just did a number of case reviews. Can you explain how you tackled such a case review?
- What did you take into account during the review? If not mentioned, ask after the use of: timeframe length, context information, starting and endpoint, coherence
- What influenced your decision to take action?
- What influenced your estimation of respiratory insufficiency?
- Why did you consider case X difficult?
- Why did you consider case X easy?
- Did you miss information to make a good estimation? What information did you miss?

Supplemental table 1. Number of participants giving a certain answer, per case. Total number of participants is 24.

	Case number:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Question	**Answer**																				
Situation?	- Improving	0	3	4	11	0	2	0	0	9	1	2	1	0	5	0	8	2	2	0	8
	- Stable	11	14	14	12	1	7	15	12	15	17	20	1	16	19	7	13	14	22	2	16
	- Deteriorating	13	7	6	1	23	15	9	12	0	6	2	22	8	0	17	3	8	0	22	0
Action required?	Yes	21	5	5	3	22	16	13	16	1	7	7	23	11	5	20	5	10	2	24	5
Expected respiratory insufficiency?	Yes	18	3	1	0	20	20	6	17	1	0	0	22	3	0	5	2	2	0	21	0
*Was respiratory insufficiency observed**		yes	yes	no	no	yes	yes	no	yes	yes	no	no	yes	no	yes	no	no	yes	no	yes	no
Difficult case?	Yes	15	10	4	5	7	14	8	13	2	7	3	5	6	2	7	7	14	7	12	2

*The actual observed occurrence of the outcome respiratory insuffiency in the hours following the data as shown to participants.

CHAPTER 5

Can continuous remote vital signs monitoring reduce the number of room visits to patients suspected of COVID-19: a quasi-experimental study

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ABSTRACT

Background – Continuous remote monitoring of vital signs on the hospital ward gained popularity during the Severe Acute Respiratory Syndrome coronavirus 2 pandemic due to its ability to support early detection of respiratory failure, and the possibility to do so without physical contact between patient and clinician. The effect of continuous monitoring on patient room visits has not been established yet. We aimed to assess the impact of continuous monitoring on the number of patient room visits for patients suspected of Corona Virus Disease 2019 (COVID-19) and the use of personal protection equipment.

Design and methods – We performed a before-after study at a ward with private rooms for patients suspected of COVID-19 at a tertiary hospital in Nijmegen, The Netherlands. Non-participant observers observed hospital staff during day, evening and night shifts to record patient room visits and personal protection equipment usage. After eleven days, wearable continuous vital signs monitoring was introduced. An interrupted time series analysis was applied to evaluate the effect of continuous monitoring on the number of patient room visits, visits for obtaining vital signs (Modified Early Warning Score visits) and the amount of personal protection equipment used.

Results – During the 45 day study period, 86 shift were observed. During each shift, approximately six rooms were included. A total of 2347 patient room visits were recorded. The slope coefficient for the number of patient room visits did not change after introducing continuous vital signs monitoring (B -0.003, 95% confidence interval -0.022/0.016). The slope coefficients of the number of Modified Early Warning Score visits and the amount of personal protection equipment used did not change either (B -0.002, 95% confidence interval -0.021/0.017 and B 0.046, 95% confidence interval -0.008/0.099). The number of Modified Early Warning Score visits did show a decline over the entire study period, however this decline was not influenced by the intervention. Evening and night shifts were associated with a fewer patient room visits compared to day shifts.

Conclusion – Introduction of continuous vital signs monitoring at a general ward for patients with suspected COVID-19 did not reduce the number of patient room visits or the usage of personal protection equipment by hospital staff. The number of Modified Early Warning Score visits declined over time, but this was not related to the introduction of continuous monitoring. Detailed analysis of the influence of continuous monitoring on the workflow of hospital staff reveals key points to increase efficacy of this intervention.

INTRODUCTION

The 2020 Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) pandemic has posed major challenges for health care centres worldwide. This virus causes a systemic disease known as Corona Virus Disease 2019 (COVID-19) with predominant signs and symptoms of upper and lower airway infection[1]. Approximately 80% of patients have only mild disease, however 20% require hospital admission for supportive care and approximately 5% require intensive care unit admission[2]. With currently over 21 million cases reported globally, this pandemic puts a significant strain on hospital organizations, medical professionals and health care supplies[3]. SARS-CoV-2 is a novel coronavirus related to Severe Acute Respiratory Syndrome coronavirus (SARS)[4] and is believed to have a similar mechanism of transmission including contact, droplet and possibly airborne transmission[5]. To limit transmission, patients with COVID-19 are isolated and being cared for using personal protection equipment. The type of personal protection equipment used differs according to the expected size and number of droplets or airborne particles emitted during a contact moment[6]. However, even with the appropriate personal protection equipment, it is recommended to reduce the time spent in close proximity of a patient with confirmed or suspected infection as much as possible to reduce the total amount of viral exposure and thus the risk of transmission[6].

Health care professionals, particularly nurses, face a dilemma when caring for patients with COVID-19 on general wards. They want to limit the amount of time spent in close proximity to the patient reducing the risk of disease transmission, but simultaneously want to stay vigilant of sudden hypoxic respiratory failure which is common in COVID-19[7,8] and might occur without symptoms of dyspnea or tachypnea[9,10]. Contact precautions in general are associated with higher adverse event rates and more delays in care[11], although this association was not confirmed by a recent systematic review on clinical deterioration that focused specifically on patients isolated for infection control[12]. A second dilemma for health care professionals is the high use of personal protection equipment compared with the imminent shortage of several personal protection equipment components, particularly Filtering Facepiece Particle (FFP) 2 masks. This results in the unique challenge of delivering the best possible care with the least possible number of visits.

A possible solution for close monitoring of patients with COVID-19 with limited patient contact is continuous remote vital signs monitoring. In recent years, continuous vital signs monitoring using wearable devices has gained interest to improve the detection of patient deterioration on the hospital ward[13–15]. Because of the possibility of wireless transfer and remote access to real time patient vital signs data, continuous monitoring was considered

as a potentially valuable addition to conventional monitoring in the care for patients with COVID-19, both at home and in health care facilities[16]. The promise of remote monitoring even prompted the Food and Drug Admistration to expand the use of certain wearable devices in order to ease the burden on health care providers[17]. However, the ability of continuous monitoring systems to support appropriate care with limited patient visits and reduction of personal protection equipment has not yet been established. The aim of this study was to assess the effect of continuous vital signs monitoring during the SARS-CoV-2 pandemic on the number of room visits of patients suspected of COVID-19, the number of visits primarily for obtaining vital signs and the amount of personal protection equipment used. We hypothesize that continuous monitoring will decrease the number of patient room visits, both primarily for obtaining vital signs and in total, and that it will consequently decrease the amount of personal protection equipment used.

METHODS

Study design and setting

We performed an observational before-and-after study of the introduction of continuous remote vital signs monitoring at the Radboud University Medical Centre, Nijmegen, The Netherlands, a tertiary hospital with a capacity of 1065 beds, lasting March 28 through May 10, 2020 (44 days). The study was conducted at a general ward with private rooms that was designated for patients suspected of COVID-19. The ward consisted of eleven single occupancy rooms (supplemental figure 1). Admission of patients was based on clinical presentation and/or CT-scan suspected for COVID-19. After confirmation of the SARS-CoV-2 infection by reverse transcription polymerase chain reaction test, the patient was transferred to a different COVID-19 cohort ward. Patients who tested negative twice and had no specific radiologic findings were transferred to a regular hospital ward and excluded from further evaluation. Between April 7 and April 10, the study ward was gradually equipped with a continuous remote monitoring system. Most staff on the ward had no experience with the continuous monitoring system. Data were prospectively collected before, during and after introduction of the system. Research evaluating continuous monitoring on the general ward was approved when introduced in 2018 in the hospital (Committee on Research Involving Human Subjects 2018-4330). Additional ethical approval for this study was waived by the institutional review board, under Dutch law. Since no personal data or patient data were collected for this study, informed consent was not required under hospital policy and the Dutch law.

Conventional vital sign measurements

Before introduction of the continuous monitoring system nurses intermittently registered respiratory rate, peripheral oxygen saturation, heart rate, systolic and diastolic blood pressure and core temperature in the electronic medical record. Measurements were obtained using an automated blood pressure measuring device and pulse oximeter (Dinamap, GE Healthcare, Germany), and a tympanic thermometer (Genius 3, Medtronic, United States of America). In addition, supplemental oxygen delivery (L/min) and consciousness using a modified AVPU score (Alert, Delirious, Voice, Pain or Unresponsive) were noted and the Modified Early Warning Score was calculated by the computer, according to the hospital protocol (table 1)[18]. This protocol stipulates a vital sign measurement every 8 hours in all patients and every 4 hours in patients with mid-range Modified Early Warning Score (3-5) or when caregivers are worried. A high Modified Early Warning Score (6 or higher), requires hourly measurements and consultation of the ward physician or consideration of rapid response team involvement.

Table 1. Weighted contribution of vital parameters of the Modified Early Warning Score.

Score points	3	2	1	0	1	2	3
Oxygen delivery, L/min				None	< 5	≥ 5	
Oxygen saturation, %	≤ 91	92-93	94-95	≥ 96			
Respiratory rate, /min	≤ 8		9-11	12-20		21-24	≥ 25
Heart rate, /min	≤ 40		41-50	51-90	91-110	111-130	≥ 131
Systolic blood pressure, mmHg	≤ 90	91-100	101-110	111-219			≥ 220
Consciousness				A		D	V/P/U
Core temperature, Celsius	≤ 35.0		35.1-36.0	36.1-38.0	38.1-39.0	≥ 39.1	

A: alert, D: delirious, V: verbal, P: pain, U: unresponsive.

Continuous vital signs monitoring system

Continuous vital signs monitoring was performed using VisiMobile® (Sotera Wireless, San Diego, California, USA). This wrist-worn device continuously measures respiratory rate, peripheral oxygen saturation, heart rate, blood pressure and skin temperature. Once every minute all vital signs, except skin temperature, were sent automatically to the electronic medical record and available to nurses for periodic validation and storage. A manually obtained temperature, the amount of supplemental oxygen delivery and the score for consciousness were added to allow the computer to calculate a Modified Early Warning Score. Real-time measurements were visible on monitoring screens at the nurse stations with the possibility to view vital signs data and trends of the preceding 96 hours. If a vital parameter exceeded preset thresholds, the system provided a single channel alarm on the monitor. All nurses at the study ward followed a learning module before the

system was implemented. The first part consisted of a custom made e-learning covering the technical and functional aspects of the system. The second part was a two hour practical skills training given by a continuous monitoring 'nurse super user'. This training included connecting the wrist device, cables and patches, blood pressure calibration, checking the appropriate displaying of vital signs on the device and monitor, and authorization of vital signs in the electronic health record. Finally, nurses practiced the entire procedure with a patient while observed and debriefed by experienced colleagues, until they were able to perform the procedure sufficiently. A day and night medical and IT help and service desk was available during the study.

Data collection

Four medical students prospectively collected the data about the number of room visits and the use of personal protection equipment by observing hospital staff during their shift at the study ward. Only hospital staff was observed, including included physicians, nurses and supportive personnel (e.g. cleaning staff and transportation). Visits by family were not recorded. All students have had basic training in conducting clinical research and were familiar with care processes at a general ward from several clinical clerkships. They were briefed about the study protocol and the case record form by the researchers before the start of the study. The students could use the same help desk as the nurses regarding questions and problems during the study. Eight hour day, night or evening shifts were covered, based on the availability of the students. Every shift, one student would function as a non-participating observer. This student randomly selected three to four nurses for observation. Together, these nurses took care of approximately six patients who were admitted to patients rooms located at one hallway (supplemental figure 1). Students approached the nurses at the beginning of their shift asking to inform them each time they planned entering a room. Because of their strategic position in the middle of the hallway they were able to control for any unannounced visit by any personnel. Data were collected per observed patient room, defined as 'an individual patient room that is observed during one shift'. When using a complete set of one mask, one apron and one pair of gloves this was registered as one patient room visit. Before each visit, the medical student asked the staff member the question: "Would you still have entered the patient room if this was not for the Modified Early Warning Score?" If the answer was yes, the visit was counted in the total number of visits. If the answer was no, the visit was counted in the total number of visits and as separate 'Visit due to Modified Early Warning Score' (MEWS visit). The total amount of used personal protection equipment by all hospital staff members was noted per patient room and during each shift. No personal data of the patients or hospital staff was recorded. Data were collected on a paper-based case report form and entered into the database by the medical student at the end of each shift. The form included an instruction part and was piloted by the four students and researcher

(YE) after which minor text were changed. The database was checked for inaccurate entries before analysis (HMRvG).

Study endpoints

The primary endpoint of this study was the total number of room visits. Secondary endpoints were the total amount of personal protection equipment used and the number of room visits for obtaining vital signs (MEWS visits).

Statistical analysis

Variables were checked for normality using the Shapiro-Wilk test. In descriptive statistics, the nonparametric variable 'Visits per room per shift' is expressed as median with interquartile ranges (IQR). Discrete variables (e.g. number of individual patients, number of shifts) are expressed as numbers with percentages. Multiple imputation was used to correct for missing values in the variable 'patients per nurse'. An interrupted time series analysis with a negative binomial regression model was performed to analyse the association between continuous monitoring and the number of patient room visits over time[19]. A slope change was chosen based on the expected effect of the intervention; a gradual decline in patient room visits[20]. The slope after was derived from the slope before and the slope change, in accordance with the primary model. More information on the statistical model formula of interrupted time series analyses can be found in the article by Bernal et al[20]. A generalized estimating equations analysis with exchangeable correlation structure was used to correct for repeated measurements within the same patient. The before period was defined as all observed patient rooms before introduction of the continuous monitoring system. The intervention period was defined as all observed patient rooms after April 7th, the day the intervention was introduced. The analysis was also performed using a model that did not include the transitional period; this did not improve the fit of the model. Due to the number of time points (97), the study had enough power to detect an estimated effect size of a minimum of 34% reduction[21]. The outcome is expressed as the degree of change per time point (beta coefficient, B), with a confidence interval (CI) and p-value. Residual plots were used to check the fit of the model. Data packages Microsoft Excel 2016 and SPSS version 25.0.0.2 were used for analysis. A two-sided alpha of 0.05 was considered statistically significant.

RESULTS

Table 2 offers an overview of the observed shifts. A total of 519 patient rooms were observed during 86 shifts. Eleven of the shifts were studied during the transition period of four days and therefore included both intermittent and continuous monitored patients. Three patients switched from intermittent to continuous monitoring during the introduction of the monitoring system. Two patients received continuous monitoring but were switched to intermittent monitoring; the reasons for switching were not recorded. After implementation of the continuous monitoring system, the nurse-to-patient ratio was lower, with 70.6% of the nurses caring for one or two patients compared to 55.2% during the intermittent monitoring period. The distribution of shift types before and after implementation was comparable.

Table 2. Description of observed shifts.

	Total	Intermittent monitoring	Continuous monitoring
Number of individual patients*	209	93	121
Number of shifts	86	32	65
Day	34 (39.5%)	12 (37.5%)	26 (40.0%)
Evening	36 (41.9%)	14 (43.8%)	27 (41.5%)
Night	16 (18.6%)	6 (18.8%)	12 (18.5%)
Number of observed patient rooms	519	172	347
Nurse-to-patient ratio total			
1:1	167 (32.2%)	27 (15.7%)	140 (40.3%)
1:2	173 (33.3%)	68 (39.5%)	105 (30.3%)
1:3	30 (5.8%)	23 (13.4%)	7 (2.0%)
1:4	4 (0.8%)	4 (2.3%)	0 (0.0%)
unknown	145 (27.9%)	50 (29.1%)	95 (27.4%)

*Five patients were counted in the intermittent and continuous monitoring period at different time point.

As shown in the descriptive results in table 3, a total of 2347 patient room visits were registered during the study period, with a median of 4 (IQR 2-5.5) visits per room per shift during the intermittent monitoring period compared to a median of 5 (IQR 3-6) visits during the continuous monitoring period. This rise in room visits after introduction of the monitoring system was most evident during the day shifts. Of the 2347 room visits, 213 (9.1%) were visits for obtaining vital signs to calculate a Modified Early Warning Score (MEWS visits). This percentage decreased from 14.1% before to 6.9% after introduction of continuous monitoring. The decrease in MEWS visits was evident during all shifts. The median number of used personal protection equipment per room per shift increased from 15 (IQR 8.5-22) to 19 (IQR 12-25).

Table 3. Descriptive results of number of room visits, number of MEWS visits and amount of PPE used.

	Total	Intermittent monitoring	Continuous monitoring
Room visits			
Total			
• Total	2347	711	1636
• Per patient room*	4 (2-6)	4 (2-5.5)	5 (3-6)
• MEWS visits	213 (9.1%)	100 (14.1%)	113 (6.9%)
Day visits			
• Total	1188	328	860
• Per patient room*	6 (5-8)	6 (4-8)	7 (5-8)
• MEWS visits	96 (8.1%)	39 (11.9%)	57 (6.6%)
Evening visits			
• Total	802	258	544
• Per patient room*	3 (2-5)	3 (2-4)	3 (2-5)
• MEWS visits	80 (10.0%)	42 (16.3%)	38 (7.0%)
Night visits			
• Total	357	125	232
• Per patient room*	2.5 (2-4)	3 (2-4)	2 (2-4)
• MEWS visits	37 (10.4%)	19 (15.2%)	18 (7.8%)
Used personal protection equipment			
• Total	9441	2870	6571
• Per patient room*	16 (10-24)	15 (8.5-22)	19 (12-25)
• MEWS visits	647 (6.9%)	306 (10.7%)	341 (5.2%)

*Median (interquartile range).
PPE: personal protection equipment. MEWS visit: a visit primarily for obtaining vital signs to be able to calculate the Modified Early Warning Score.

Although a difference in number of room visits before and after intervention was observed in the descriptive results, the interrupted time series analysis (table 4) did not show an association between continuous vital signs monitoring and the total number of room visits, as demonstrated by an insignificant slope change of -0.003 (95% CI -0.022-0.016, p-value 0.761). Correspondingly, the number of used personal protection equipment was not affected (B -0.002 (95% CI -0.021-0.017, p-value 0.835)). Both outcomes, however, were influenced by the type of shift; evening and night shifts were associated with a reduction in the number of room visits and personal protection equipment usage, in contrast to day shifts. For the number of MEWS visits, a significant decline over time was found, both before and after the intervention. However, continuous monitoring did not impact this decline (B 0.046 (95% CI -0.008-0.099, p-value 0.097)) and even slightly increased the number of MEWS visits (B 0.614 (95% CI 0.000-1.228, p-value 0.050)). The evening was the only shift type that had a significant association with the number of MEWS visits (B -0.427 (95% CI -0.760- -0.093, p-value 0.012)). A graphic depicture of the slope changes over time is shown in figure 1.

Table 4. Interrupted time series analysis.

	Total number of room visits			Total used PPE			Total number of MEWS visits		
	B	**95% CI**	**p-value**	**B**	**95% CI**	**p-value**	**B**	**95%CI**	**p-value**
Day shift*	Reference								
Evening shift	-0.712	-0.879 / -0.545	0.000	-0.538	-0.645 / -0.431	0.000	-0.427	-0.760 / -0.093	0.012
Night shift	-0.536	-0.640 / -0.432	0.000	-0.722	-0.892 / -0.552	0.000	-0.385	-0.944 / 0.174	0.177
Nurse-to-patient ratio	-0.048	-0.136 / 0.040	0.260	-0.053	-0.145 / 0.039	0.235	-0.104	-0.330 / 0.122	0.366
Intermittent monitoring*	Reference								
Continuous monitoring	0.105	-0.065 / 0.275	0.226	0.112	-0.059 / 0.282	0.200	0.614	0.000 / 1.228	0.050
Slope before	0.001	-0.170 / 0.018	0.949	-0.001	-0.018 / 0.016	0.915	-0.105	-0.154 / -0.057	0.000
Slope change	-0.003	-0.022 / 0.016	0.761	-0.002	-0.021 / 0.017	0.835	0.046	-0.008 / 0.099	0.097
Slope after	-0.002	-0.010 / 0.005	0.521	-0.003	-0.010 / 0.004	0.435	-0.059	-0.088 / -0.031	0.000

* Day shift and Intermittent monitoring were used as reference values in the model.

PPE personal protection equipment; MEWS Modified Early Warning Score; CI confidence interval, B beta-coefficient (the degree of change per time point).

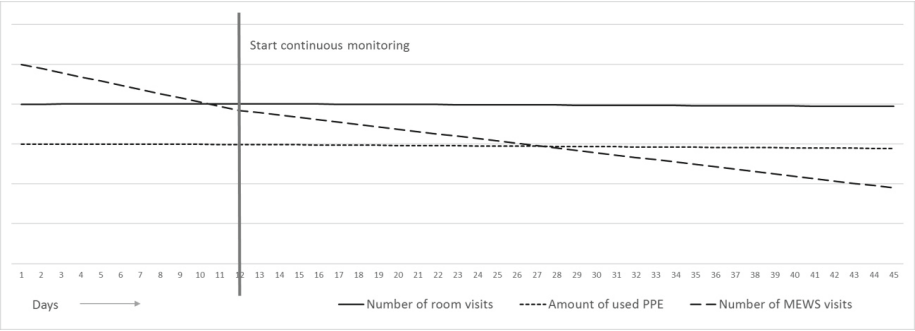

Figure 1. Graphic depicture of the interrupted time series analysis. PPE personal protection equipment; MEWS Modified Early Warning Score.

DISCUSSION

Although remote monitoring systems are claimed to reduce patient room visits by nurses with 30-50%[22], no scientific evidence is supporting these claims so far. In contrast with our hypothesis, this study demonstrates no impact of continuous monitoring on the number of patient room visits or personal protection equipment usage when corrected for shift type, which does influence patient room visits. Even though the number of MEWS visits decreased over time, this was not the result of continuous vital signs monitoring.

Studies on the number of patient room visits are rare, however in a study by Cohen et al. in 2012, conducted on several wards of academic hospitals, the number of patient room visits was a tenfold higher compared to our study[23]. Isolated patients received a median of 5 visits per hour in their study[23] but only a median of 4 visits per eight hours in our study. Differences in defining room visits and case-mix might explain the higher numbers. We did not include visits by relatives and other personal visitors, which was about one-quarter of the total number of visits in the study by Cohen et al.[23]. Notably, hospital policy restricted visits by relatives to one per day at our study ward. Only the day shifts were studied by Cohen et al., which was the shift with the highest number of room visits in our study. Although they did look at differences between intensive care units and general wards, and isolated patients and non-isolated patients, Cohen et al. did not report on numbers on isolated patients on the general ward specifically, the kind of patients that were included in our study.

According to previous research, assessment of patients and obtaining vital signs takes up only seven percent of nursing practice time[24], but is the reason for 49% of nurse-patient interactions[25]. We expected a high number of MEWS visits for patients with

COVID-19 signs and symptoms due to the severity and erratic course of the disease, and given that all patients were in private rooms; multi-patient rooms make it possible to combine taking vital signs of several patients in one visit. Moreover, we expected a decrease in both MEWS visits and room visits after introduction of continuous vital signs monitoring. Although the percentage of MEWS visits was halved, this had no effect on the total number of patient room visits; this number even increased slightly. Most likely, vital sign measurements were not only taken during MEWS visits, but also during visits with a different primary purpose, such as providing medication or assisting in personal hygiene. These vital sign measurements were not captured in this study. The ability of nurses to combine multiple tasks in one visit, thus effectively limiting the number of patient room visits themselves, has probably affected the impact of continuous monitoring. Conversely, rooms may have been entered due to deviant vital signs on the nurse monitors that needed to be checked at the bedside, which would lead to an increase rather than a decrease in MEWS visits. An increase in MEWS visits as a results of increased alertness by nurses, triggered by rapidly changing vital signs of these patients seen on the remote monitors, could be considered a benefit of remote continuous monitoring.

The continuous decline of the number of MEWS visits might be explained by two learning curves: nurses learning to use the continuous monitoring system, and all clinicians learning to manage a new infectious disease, COVID-19. Deploying a continuous monitoring system on the ward requires skills training and frequent practice until proficiency. Previous research shows that nurses perceived a higher value of continuous monitoring in their decision making if they are trained and confident in its use[26,27]. Also, technical issues and false alarms are likely to decline and are solved during a planned room visits when nurses become more acquainted with the monitoring system. As the pandemic progressed, more information became available about the disease manifestations, and clinicians gained more experience with both patients with COVID-19 and continuous vital signs data. This resulted in more confidence interpreting changes in vital signs and decisions whether or not to (de)escalate care, supported by continuous data. Altogether this may have affected both MEWS visits and total number of patient room visits in either direction.

Although a decrease in patient room visits is desirable for limiting disease transmission and personal protection equipment usage, it can amplify patients' feelings of social isolation. The number of patient room visits is reportedly lower in isolated non-COVID-19 patients[11]. High rates of depression and anxiety are found associated with private room isolation[11,28]. Remote vital signs monitoring system may further deprive social contact, an important concern raised by patients and clinicians previously[29,30]. Obviously, feelings of social deprivation are dependent not only on nurse-patient contacts but also

contact with relatives and other patients, which were very limited for most patients suspected of COVID-19.

Limitations

The most prominent limitation of this study is the before-after design in a highly dynamic hospital environment with an unknown disease in the beginning of this pandemic. Although the hospital ward population was uniform, all patients suspected of COVID-19, the workflow and protocols on the ward were affected by the increasing knowledge on COVID-19 and the rapidly changing (inter)national guidelines. The used statistical strategy partly compensated for this, however we could only compensate for known confounders. Designs without this limitation, such as randomized controlled trials, were deemed inappropriate and have their own ethical and methodological drawbacks. Even though the hospital ward population was uniform based on disease type, the individual patients might have differed in various ways based on factors such as comorbidities and disease severity. Factors of hospital staff, such as experience, might have been of influence too. These factors were not taken into account in our study. Unexplained observations, such as the difference in nurse-to-patients before and after implementation, might also be explained by these factors. In observational studies of behaviour there is always a risk of the Hawthorne effect. Hospital staff might have behaved differently because they know they are being observed. However, we do not think this will have influenced the outcomes of our study since this effect will have been similar in both the before and after period. Besides, hospital staff was already very aware they had to limit the number of patient room visits since supplies were limited. Because of the strict isolation measures, the observers were not able to follow hospital staff into the patient rooms and register their exact activities. Although the number of visits was not altered by the continuous monitoring, the timing and purpose of the visit might have been more tailored to the patient's need. This study did not have enough data to analyse day, evening and night shifts separately. During night shifts, nurses are low in staff[31] and are less inclined to disturb patients for measuring vital signs[30]. Continuous monitoring might have a greater effect on the number of room visits during the night, however this assumption need to be confirmed in future research. Another limitation is the type of monitoring system used. The VisiMobile® is a fairly complete monitor; however, for measuring the core temperature and completing the Modified Early Warning Score the nurse still had to enter the patient's room. No wearable so far is able to measure all components of the Modified Early Warning Score[15,32], as core temperature and consciousness are technically challenging to monitor continuously by one wearable device, and more importantly as nurses' worry cannot be measured without nurse-patient interaction[33].

Future research

During the study, the course and management of COVID-19 was roughly unknown for nurses and physicians. Repeating the study in a more stable situation, after formally training all hospital staff, would be of interest during the current and following outbreaks of COVID-19 and could also improve the generalizability of the study to other patients in isolation. In addition, the number of outcomes could be extended. Except for alarm fatigue[34] few aspects of the way workflow is influenced by continuous monitoring have been studied so far. A more advanced approach that may optimize the effects of continuous vital signs monitoring for patients in isolation is integrating this technology with an audio-video system, to enable nurses to acquire situational awareness. This way the urgency to enter the room can better be determined and patient can be remotely advised and instructed. Such technology is currently less common at a hospital ward compared to an intensive care unit or a nursing home, but bears the opportunity to optimize continuous monitoring by pervasive sensing and deep learning[35]. Lastly, including the influence of multiple patient factors, such as comorbidities or functional status, and clinician related factors, such as experience or age, might improve our understanding of this complex intervention even more.

CONCLUSION

We conclude that introduction of a continuous remote vital signs monitoring system using a wearable at a ward for patients with suspected COVID-19 during the SARS-CoV-2 pandemic did not reduce the number of patient room visits or the usage of personal protection equipment by hospital staff. The number of visits for obtaining vital signs did decrease, probably due to altered nurses' workflow, more frequent observation of vital signs derangements and increased experience with disease management. Further quantitative and qualitative analyses of the influence of continuous monitoring on the workflow of hospital staff will improve our understanding of this novel intervention, and could reveal key points to increase its efficacy.

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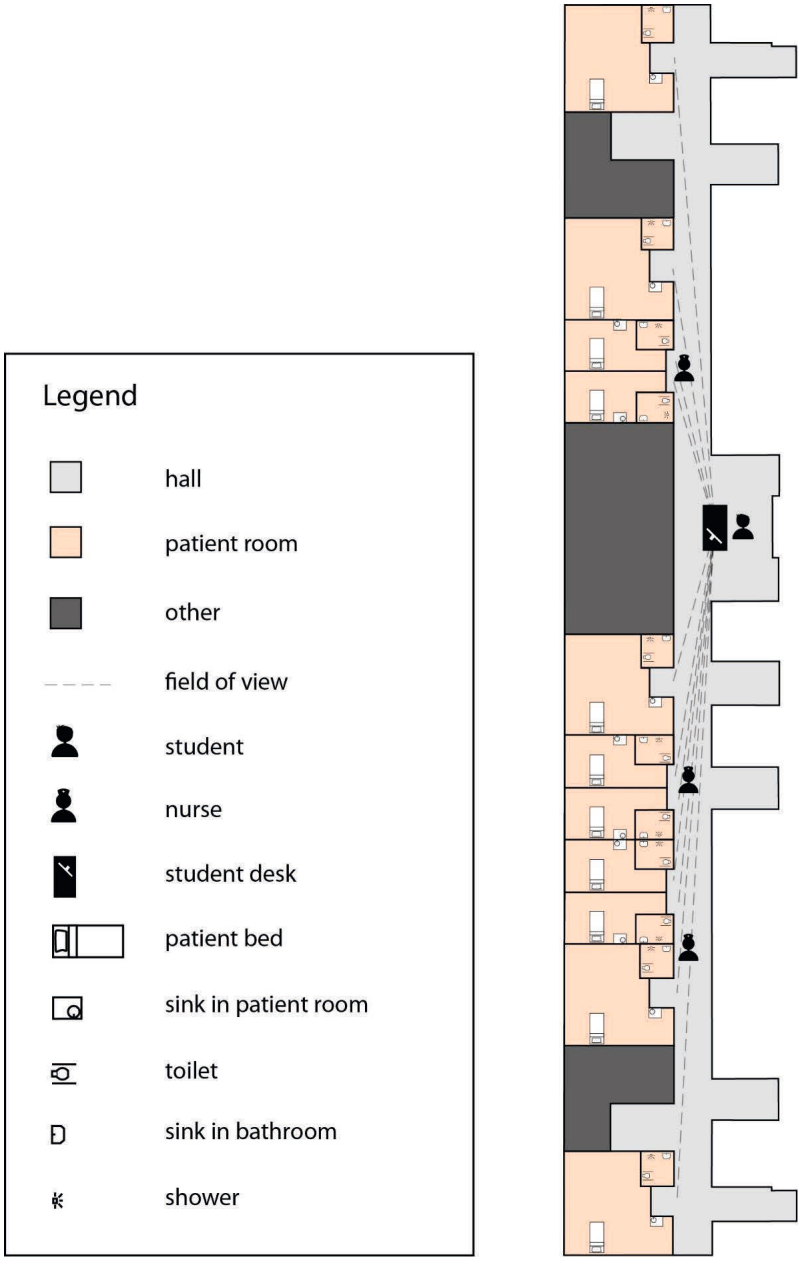
SUPPLEMENTAL MATERIAL



Supplemental figure 1. Floor plan of study ward with positioning of observer.

PART III

Remote hospital care
assisted by telemonitoring

CHAPTER 6

Remote hospital care for recovering COVID-19 patients using telemedicine: a randomised controlled trial

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ABSTRACT

Background – To ensure availability of hospital beds and improve COVID-19 patients' well-being during the ongoing pandemic, hospital care could be offered at home. Retrospective studies show promising results of deploying remote hospital care to reduce the number of days spent in the hospital, but the beneficial effect has yet to be established.

Methods – We conducted a single centre, randomised trial from January to June 2021, including hospitalised COVID-19 patients who were in the recovery stage of the disease. Hospital care for the intervention group was transitioned to the patient's home, including oxygen therapy, medication and remote monitoring. The control group received in-hospital care as usual. The primary endpoint was the number of hospital-free days during the 30 days following randomisation. Secondary endpoints included health care consumption during the follow-up period and mortality.

Results – A total of 62 patients were randomised (31 control, 31 intervention). The mean difference in hospital-free days was 1.7 (26.7 control vs. 28.4 intervention, 95%CI of difference -0.5 to 4.2, $p = 0.112$). In the intervention group, the index hospital length of stay was 1.6 days shorter (95%CI –2.4 to –0.8, $p < 0.001$), but the total duration of care under hospital responsibility was 4.1 days longer (95% CI 0.5 to 7.7, $p = 0.028$).

Conclusion – Remote hospital care for recovering COVID-19 patients is feasible. However, we could not demonstrate an increase in hospital-free days in the 30 days following randomisation. Optimising the intervention, timing, and identification of patients who will benefit most from remote hospital care could improve the impact of this intervention.

INTRODUCTION

Availability of hospital care is an ongoing challenge in the SARS-CoV-2 pandemic. Even with available vaccines, outbreaks might continue for years[1] and put pressure on hospital capacities. Particularly the need for oxygen therapy increases the length of hospitalisation and reduces the availability of beds. The addition of dexamethasone to supportive care improves the outcome but only shortens the length of stay by one day[2]. Hospitals therefore need to prepare for delivering long-term COVID-19 care while preserving regular care for other patients.

Admission for COVID-19 also has an impact on patient well-being. Family visits are limited to prevent viral spread, and patients are often transferred to referral hospitals in the case of capacity problems. Moreover, patients in contact isolation can present with depression, anxiety and anger[3]. The environment of a patient has been shown to influence a patient's psychological well-being[4] and can be improved by a feeling of 'being at home'[4,5].

To ensure availability of hospital beds while improving patients' well-being, hospital care can be offered at home. Hospital care at home has the potential to avoid admissions and reduce the length of in-hospital stay[6,7]. A pre-COVID-19 study reported a decrease of six in-hospital days per patient after implementing hospital care at home for acute patients[8]. This included daily visits by a trained nurse, which is labour intensive. Telemedicine is a less laborious alternative. Telemedicine offers healthcare-related services via electronic information and telecommunication technologies. These services can range from a single video consult to continuous remote monitoring, and these were successful in earlier studies[9]. During the pandemic, numerous hospitals have implemented telemedicine-based interventions to reduce the hospital stay for COVID-19[10–13] or avoid hospital admission at all[12,14–16]. The first retrospective studies of reducing the length of stay by remote hospital care have shown promising results[10,11], but the added value has yet to be determined in a controlled setting.

In this trial, we assessed the effectiveness of remote hospital care for hospitalised, recovering COVID-19 patients. We hypothesize that transitioning hospital care to the home situation will result in more hospital-free days, without compromising patient safety.

MATERIALS AND METHODS

Design and Setting

We conducted a non-blinded, randomised trial at the tertiary hospital in Utrecht, The Netherlands. Inclusion took place from 11 January to 7 May 2021. Since this centre was one of the primary referral centres for hospitals with capacity problems, 80% of COVID-19 patients were transfers and not necessarily in need of tertiary care. Patients were randomised 1:1 in either the intervention group or the control group. We used the block randomisation option in Castor with block sizes two, four and six (Castor Electronic Data Capture, Amsterdam, The Netherlands). The research ethics committee Utrecht approved the study (20/783). The study was registered in the Dutch Trial register (NL9081 Early@home).

Study population

Eligible patients were identified by the treating physician at the ward and approached by a member of the research team, who double checked all in- and exclusion criteria. A patient could be included if he/she had confirmed COVID-19, was at least 18 years old, had a family member or other supportive caretaker at home, had a thermometer and smartphone, was able to use the mobile application (app) and pulse oximeter (possibly with help from the supportive caretaker), and was fluent enough in Dutch to understand the app. Patients were excluded if they suffered from dementia or other illnesses that limited the expected therapy compliance, if they needed more care than could be arranged at home, if the expected discharge destination was another care facility, e.g., a rehabilitation centre, or if discharge was already pending and hospital care was no longer needed. Patients were given 24 h to consider participation. After signing informed consent, the General Practitioner (GP) was contacted to check whether the home situation was safe enough for the intervention. Randomisation was performed when the patient met all discharge criteria: a maximum of 3 L/min oxygen therapy with no increase during the last 24 h, no intravenous medication that cannot be replaced with a non-intravenous alternative, no planned diagnostic tests that needed to be performed in the hospital or could lead to in-hospital treatment, permission by the treating physician.

Care as usual

The control group received care as usual. Vital signs were checked three times daily, or more in the case of clinical instability. As a rule, patients were discharged 24 h after oxygen therapy was ceased, but the treating physician could make a substantiated decision to differ from this rule. A standard dose of dalteparin to prevent thrombosis due to immobilisation was given until discharge, and dexamethasone was given until the end of oxygen therapy, with a maximum of ten days. At the start of this trial, oxygen therapy,

dexamethasone and dalteparin administration were considered in-hospital treatments in The Netherlands.

Intervention

For the intervention group, remote hospital care was organized as soon as possible after randomisation. The hospital care provided at home, instead of in the hospital, included oxygen therapy and prescriptions for necessary medication. Visits by hospital staff were replaced with remote monitoring and telephone contact (see below). Dexamethasone and prophylactic dalteparin administration was similar to the control group, with an exception for active patients, who were no longer required to receive thromboprophylaxis. Patients received a medically certified pulse oximeter (iHealth® Air, Andon Health Co Ltd., Tianjin, China) and an account for the app (Luscii Healthtech BV, Amsterdam, The Netherlands). They received information from the Medical Control Centre (MCC), a group of trained medical students who performed the monitoring. After inclusion in the intervention group, a member of the MCC would visit the patient to inform him/her on how to use the app and to provide the patient with a manual and a personal treatment plan, including personalised thresholds for oxygen saturation.

While at home with remote hospital care, patients filled out a questionnaire in the app three times daily at predetermined moments. The questionnaire consisted of scores for coughing, shortness of breath and general well-being, temperature and oxygen saturation (supplemental figure 1). The MCC checked these questionnaires between 09:00 and 16:00, including the questionnaires from the prior evening. The patient was called immediately in the case of irregularities that required rapid action. Between 11:00 and 12:00, the MCC called all patients by telephone for a daily check-up and to communicate any changes in treatment, such as titration of oxygen therapy, changes in medication, or readmission in case of severe deterioration. A consultant in internal medicine with COVID-19 expertise supervised the MCC and was involved in all treatment decisions. If oxygen therapy was ceased for 48 h and the patients' condition was stable, the patient was discharged from hospital responsibility.

Follow-up

At 30 days after randomisation, the patient was contacted for follow-up on the number of hospital-free days. If a patient could not be reached, the GP provided the missing information.

Endpoint and Data Collection

The primary endpoint was the number of hospital-free days[17]. This patient-centred endpoint includes both the index hospital length of stay and the impact of readmissions[18–20]. The number of hospital-free days is defined as the number of days

spent alive at home in the 30 days following randomisation. For every day the patient was readmitted or was not alive after randomisation, a day was subtracted. Since emergency department (ED) visits and other unplanned hospital visits often result in a day spent in the hospital too, these were added to the score[17]. Secondary endpoints were length of hospital stay, length of hospital stay and oxygen therapy following randomisation, duration of care under hospital responsibility, number of readmissions, ED visits, other unplanned hospital visits and GP contacts, and mortality. Care under hospital responsibility was defined as the total number of days a patient was under the responsibility of the hospital, either in the hospital or at home with remote hospital care. If the end of treatment was not reached by the time of follow-up, the follow-up date was registered as end-date. To describe the cohort, admission information and patient characteristics were documented, including the Charlson Comorbidity Index[21] and Clinical Frailty Scale score[22].

Sample Size

Since the primary outcome was expected to be left skewed (most patients will reach a high number of hospital-free days), the sample size was determined using 1000 simulations based on the Mann–Whitney U test. We based the power on a one-day difference, the minimal clinically relevant difference. Since we assumed some variety in the effect of the intervention, we added a distribution of hospital stay following randomisation in both groups (supplemental table 1). Previous studies showed a readmission rate of 2.2–18% (mean 9%)[23–26]. Since our study did not include patients who were discharged to a nursing home or rehabilitation centre, which is one of the primary risk factors for readmission[26], we assumed a lower readmission rate of 5%. For the intervention group, we assumed a readmission rate of 9%[27]. We assumed a mean readmission length of 5 days. Mortality was not accounted for since the expected mortality in this population of recovering patients was low. With these assumptions, 80% power and a two-sided alpha of 0.05, a sample of 62 patients was needed.

Statistical analysis

Primary analysis was based on intention-to-treat. Given the skewed distribution, we used the bootstrap *t*-test with 10,000 iterations to calculate the mean difference in number of hospital-free days with a 95% confidence interval[28]. The same approach was used to compare the secondary endpoints for duration of care. The Wald statistic was used to test the difference in the number of GP contacts. Since the study was highly underpowered to find differences in the remaining secondary endpoints, these results were presented descriptively. A per-protocol sensitivity analysis was performed since not all patients were treated as intended. Because an increasing number of patients in the control group were discharged with oxygen therapy at home, which is not a complete intervention but

also differs from usual care, we looked at the characteristics of this group separately. A two-sided alpha of 0.05 or lower was considered statistically significant. RStudio version 4.0.3 was used for all analyses.

RESULTS

Of the 226 patients selected by the ward physicians, 48 did not meet the inclusion criteria at the second evaluation. Another 27 patients did not feel safe towards the idea of remote hospital care, and 41 patients did not consent for other or unknown reasons. Three patients agreed to participate but dropped out before randomisation (figure 1). Ultimately, 62 patients were included. One patient changed his mind after learning he was randomised to the intervention group and was discharged home using the usual care route. Baseline characteristics of participating patients are shown in Table 1. The included patients were relatively young and had few comorbidities.

Table 1. Cohort description.

	Control (*n* = 31)	**Intervention (*n* = 31)**
Patient		
Age (mean, sd)	55.4 (13.2)	55.1 (7.5)
Female (%)	13 (41.9%)	14 (45.1%)
CFS * (mean, sd)	2.1 (1.3)	2 (0.6)
Active smoker (%)	0 (0%)	1 (3.2%)
Hypertension (%)	5 (16.1%)	6 (19.4%)
Cardiovascular disease (%)	3 (9.7%)	2 (6.5%)
CCI ** (median, IQR)	2 (0–3)	1 (1–2)
Index admission		
Transferred from a different hospital (%)	26 (83.9%)	28 (90.3%)
Admitted to ICU (%)	3 (9.7%)	4 (12.9%)
Length of hospital admission before randomisation (median, IQR)	6 (4.5–9)	6 (4–8.5)
Pulmonary embolism (%)	3 (9.7%)	2 (6.5%)
Bacterial superinfection (%)	3 (9.7%)	2 (6.5%)
Other (%)	1 (3.2%)	3 (10%)
Dexamethasone or prednisone treatment (%)	31 (100%)	31 (100%)
Highest delivered FiO2 at ward (median, IQR)	0.44 (0.36–0.6)	0.4 (0.36–0.6)
Oxygen therapy at randomisation (L/min) (mean, sd)	2.0 (1.0)	2.1 (0.9)
Discharged from hospital care with oxygen therapy (%)	5 (16.1%)	1 (3.2%)

* CFS—clinical frailty scale, ** CCI—Charlson comorbidity index. ^ One patient in the intervention group was discharged from hospital care while on oxygen therapy; she was handed over to the outpatient clinic of her own pulmonologist.

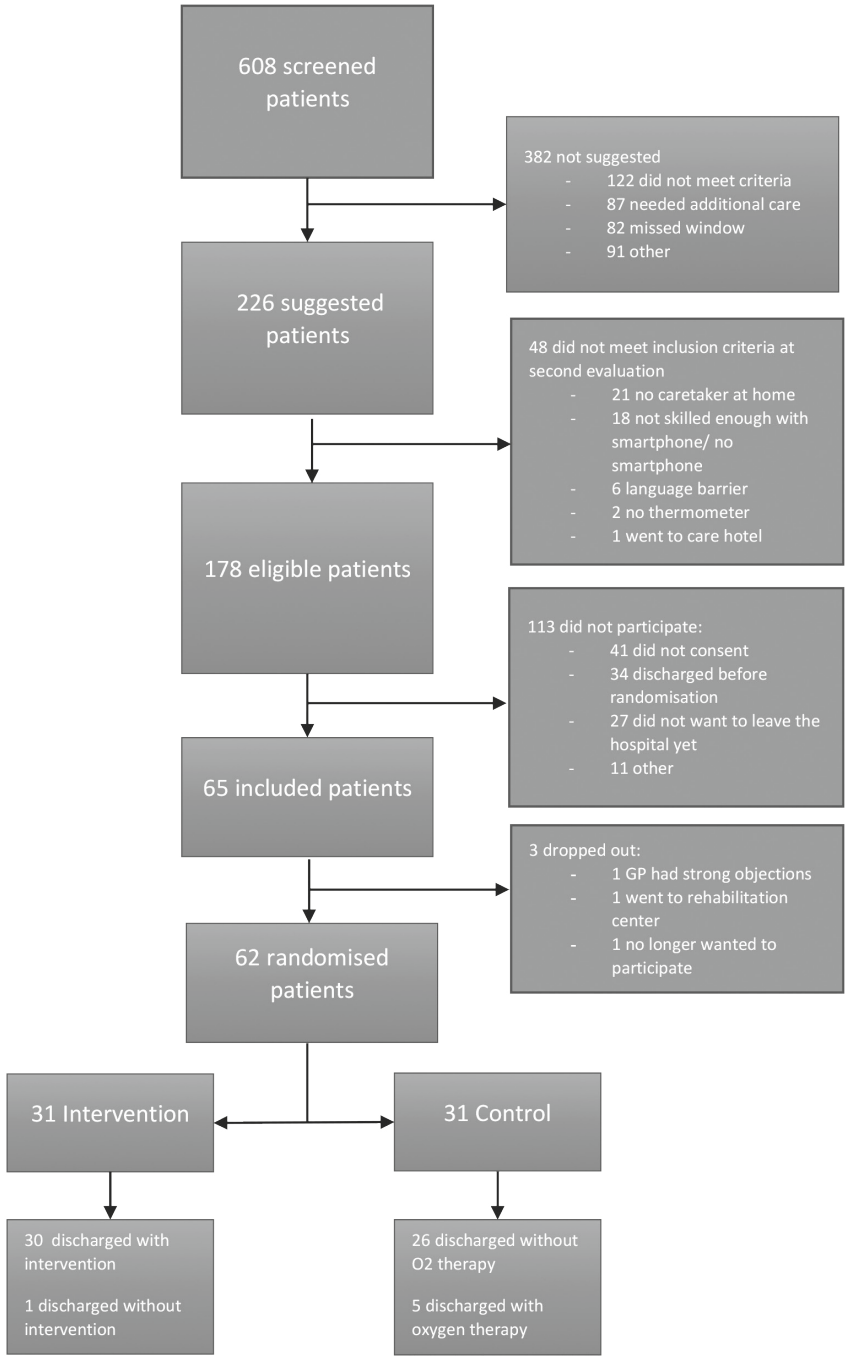

Figure 1. Flowchart of study inclusion. GP—general practitioner.

As shown in table 2, the mean difference in hospital-free days between the two groups was 1.7 days (95% CI −0.5 to 4.2, $p = 0.112$) but was not statistically significant. This result was not altered by the per-protocol analysis (difference of 1.7 (95% CI −0.6 to 4.2, $p = 0.126$)). The distribution of hospital-free days is shown in figure 2. We observed several differences in secondary endpoints. Patients in the intervention group had a shorter index admission stay following randomisation and were able to go home 1.6 days earlier than patients in the control group. In contrast, they received longer oxygen therapy and care under hospital responsibility than the control group (table 2). We found no difference in the number of days in the hospital or death after index admission. Patients in the control group made 2.4 times more visits to the GP, mostly for COVID-19 (table 2). Twenty-five patients in the intervention group recorded one or more values below the threshold for oxygen saturation while at home, and eighteen patients recorded an oxygen saturation of 92% or lower at some point during remote monitoring.

Table 2. Comparison of main outcomes.

	Control (*n* = 31)	**Intervention (*n* = 31)**	**Difference (95% CI)**	***p*-value**
Hospital-free days in 30 days following randomisation (mean, sd)	26.7 (5.7)	28.4 (3.8)	1.7 (−0.5 to 4.2)	0.112 *
Index hospital length of stay (mean, sd)	10.0 (7.0)	7.3 (4.3)	−2.7 (−5.7 to 0.0)	0.045 *
Duration of index hospital stay after randomisation (mean, sd)	2.3 (2.3)	0.7 (0.9)	−1.6 (−2.4 to −0.8)	<0.001 *
Number of days in hospital or dead following index hospital stay (mean, sd)	1.0 (3.7)	0.9 (3.7)	−0.1 (−2.1 to 1.8)	0.906 *
Duration of hospital responsibility (hospital stay + hospital care at home) (mean, sd)	10.0 (7.0)	14.1 (7.6)	4.1 (0.5 to 7.7)	0.028 *
Days of oxygen therapy following randomisation (mean, sd)	3.4 (7.5)	6.7 (7.5)	3.3 (−0.5 to 6.8)	0.101 *
ED visits (N, %)	1 (3.2%)	3 (9.7%)	–	–
- For COVID-19	1	3		
Other unplanned hospital visits (N, %)	2 (6.5%)	2 (6.5%)	–	–
- For COVID-19	2	2	–	–
Readmission (N, %)	1 (3.2%)	2 (6.5%)	–	–
- For COVID-19	1	2		
GP visits (N, %)	20 (64.5%)	12 (38.7%)	–	0.035 †
- For COVID-19	19	8		
Telephone contact with GP by patient (%)	22 (71.0%)	25 (80.6%)	–	0.371 †
Mortality (%)	1 (3.2%)	0 (0%)	–	–

* Bootstrap *t*-test with 10,000 iterations; † risk ratios with Wald statistic; sd—standard deviation; ED—emergency department; GP—general practitioner.

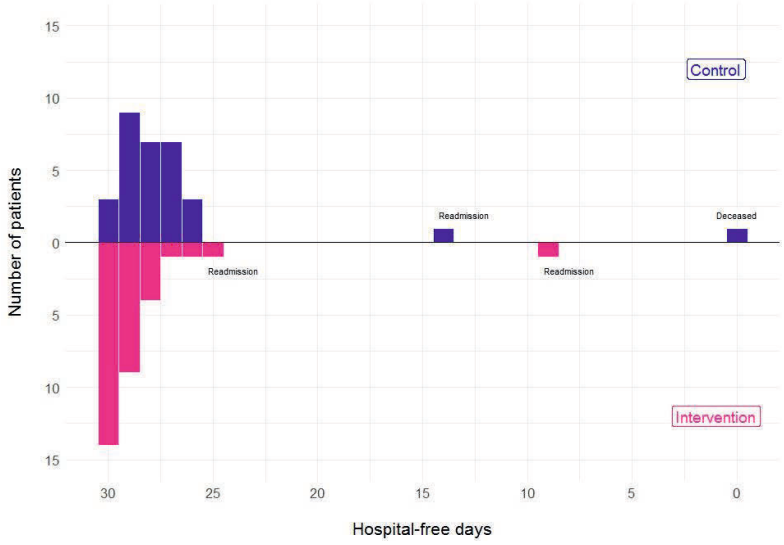

Figure 2. Distribution of number of hospital-free days 30 days after randomisation.

Five patients in the control group received oxygen therapy at home. Baseline characteristics were comparable with the rest of the cohort. The patients were discharged 0–3 days after randomisation; they reached a number of hospital-free days of 27, 27, 29, 29 and 30 days. All of these patients visited their GP and none of them were readmitted or presented at the ED.

DISCUSSION

In this study, we assessed the effectiveness of remote hospital care for recovering COVID-19 patients. Although remote hospital care using telemedicine was feasible, we were unable to show a significant increase in hospital-free days. The initial reduction in index length of stay did not result in a significant difference in hospital-free days after 30 days, probably due to a different distribution in hospital-free days than expected.

Comparison with previous research

The reduction in length of index admission of 1.6 days was smaller than reported previously[10,11]. The difference in effect size between studies is most likely caused by the difference in duration of oxygen therapy inside and outside the hospital. Previous studies counted every day of oxygen therapy at home as a reduction in hospital length of stay. Our study shows that oxygen therapy was tapered down more slowly at home than at the hospital. If all these days are counted as a reduction in hospital stay, the effect size could be overestimated. Secondly, we found that it was difficult to predict the duration of

oxygen therapy, making it hard to determine which patients would benefit from remote hospital care. If future research can identify those patients who will benefit most, the impact of the intervention might be higher. Furthermore, contamination of the control group in our study has occurred. As the study progressed, clinicians recognized that earlier discharge was possible and applied this to the control group too, sometimes even with oxygen therapy at home. Disappointment of patients in the control group might have amplified this since they often asked if they could leave the hospital early anyway after learning the outcome of randomisation. This is highlighted by our observation that oxygen therapy in the control group was tapered down in one day, even though mean oxygen administration at randomisation was 2L/min.

Although the index admission was shorter, the total length of care under hospital responsibility was longer in the intervention group. This was partly due to protocol. Patients in the control group were discharged as soon as the treating physician saw fit, but patients in the intervention group were only discharged two days after oxygen therapy was ceased. However, a prolonged length of hospital responsibility is not necessarily a negative outcome. The number of GP visits for COVID-19 was more than two times higher in the control group, indicating a need for patients to be in contact with a physician following hospital admission. While tapering oxygen therapy took longer at home, patients were more in charge of their own therapy. Given the regular low values for oxygen saturation in the intervention group, COVID-19 patients in general might benefit from a more gradual tapering of oxygen therapy, something that cannot be accomplished in a pressured hospital environment. Remote hospital care could be an intermediate step between the hospital and home, giving patients a little more time to recover and regain confidence in their bodies. Earlier studies report that patients appreciate the intervention, feel safe at home, and would recommend it to others[11,27].

Strengths and limitations

Several retrospective studies studied the effect of remote hospital care for recovering COVID-19 patients, but this is the first study to compare the intervention in a controlled randomised setting. Although this was a single centre study in a tertiary hospital, the majority of patients were allocated from hospitals across the country, creating a varied population. The fluctuating case-loads during the pandemic interfered with the study. Variable hospital capacity might have influenced decision making by physicians. As the pandemic progressed, clinicians gained confidence in treating COVID-19 patients, resulting in faster tapering of oxygen therapy and more patients being discharged with oxygen therapy. Unfortunately, blinding was not possible, which resulted in contamination. The predetermined variation of the expected effect size will only have partially corrected for this. Although this randomised trial was designed with practicality in mind, the

artificial circumstances might have led to a delay in randomisation, for example, due to the mandatory 24 h consideration period. Furthermore, some patients were willing to participate in the intervention but not in a study setting, leading to selection bias.

Even though we found no evidence that the intervention was unsafe, this finding should be interpreted with caution. Major differences in safety would have influenced the primary endpoint and would have become apparent even in a small population. However, our study was not powered to find definite differences in mortality or readmission rate, for which much larger trials would be needed.

Implications for future research

The basic elements of this intervention (oxygen therapy and medication at home combined with remote monitoring) can be used in a variety of countries and settings. All over the world, remote monitoring has already been implemented for this purpose[29–32], and several have added home treatment using comparable inclusion criteria[12,23,31], showing the high level of feasibility. Nevertheless, the intervention is only feasible in a limited group of patients. In all studies, the patients included were relatively young, healthy, and capable of adequate communication with hospital staff[10–12]. Only 8% of all admitted patients in the study of van Herwerden et al. and 10% of the admitted patients in our study ultimately received remote care. Several steps could be taken to expand usability. The intervention could be made suitable for more patients, for example elderly, by making the app more accessible or less vital. Secondly, if we could predict who will benefit most of this intervention, the success rate could be improved. Lastly, the timing of the intervention could be optimized. Since a considerable number of eligible patients were discharged before inclusion could take place, the inclusion criteria might have been too strict. Nonetheless, the effect of these alterations on the safety of the intervention should be carefully monitored.

CONCLUSION

In conclusion, remote hospital care for recovering COVID-19 patients was feasible, but we were unable to show an increase in the number of hospital-free days 30 days after randomisation. By optimising the intervention, the timing of the intervention, and identification of those patients who will benefit most, the impact might be considerably improved.

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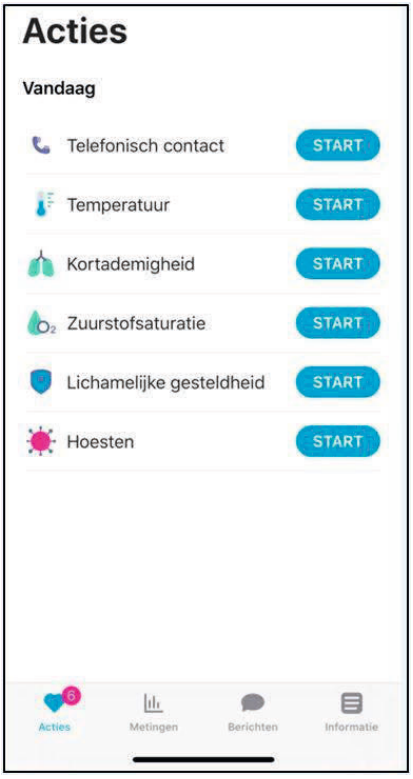
SUPPLEMENTAL MATERIAL



Supplemental figure 1. App questionnaire.

Supplemental table 1. Assumed distribution of days until discharge. (T=0 is day of randomization).

Discharge on day T=	Intervention	Control
1	40%	0%
2	30%	10%
3	20%	40%
4	10%	50%

CHAPTER 7

Designing a virtual hospital-at-home intervention for patients with infectious diseases: a data-driven approach

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ABSTRACT

Rationale – Virtual hospital-at-home care might be an alternative to standard hospital care for patients with infectious diseases. In this study, we explore the potential for virtual hospital-at-home care, and the components of care needed to be organized for this population.

Methods – A retrospective cohort study of internal medicine patients suspected of infectious diseases, admitted between January 1st and December 31st 2019. We collected information on delivered care during 4 periods: emergency department visit, the first 24h, between 24-72h, and after 72h of admission. Care components that could be delivered at home were combined into care packages, and the potential number of eligible patients per package was described. The most feasible package was described in detail.

Results – 763 patients were included, mostly referred for the general internal medicine (35%) and most common diagnosis was lower respiratory tract infection (27%). Most frequently administered care components were laboratory tests, non-oral medication, and intercollegiate consultation. With a package consisting of telemonitoring, video consultation, non-oral medication administration, laboratory tests, oxygen therapy, and radiological diagnostics, 48% of patients was eligible for hospital-at-home care, with 35% already eligible directly after emergency department visit. Higher age, higher early warning score at presentation, presentation by ambulance, and admission for general internal medicine decreased the chance of being eligible.

Conclusion – While the potential for virtual hospital-at-home care is high, it depends greatly on which care components can be arranged. With a relatively compact package, virtual hospital-at-home care could potentially be offered to 48% of internal medicine patients admitted with suspected infection.

INTRODUCTION

The aim of hospital-at-home care is to provide hospital-level care in the patient's home in a situation that would otherwise require hospital admission[1]. Beside creating a more positive healing environment for the patient[2], hospital-at-home interventions might reduce costs and resources[3]. It might also be a favourable alternative to hospitalization for frail elderly patients with a high risk of hospital complications, such as delirium[4]. Hospital-at-home has been used for decades for various populations and in a wide range of modalities[3]. Most of these interventions include in-person visits by hospital staff (nurses and/or physicians), which still requires considerable (human) resources. An alternative for in-person care could be telemedicine, where part of – or potentially all – the home visits are substituted with virtual visits and telemonitoring of vital signs. This type of care has previously proven to be feasible and satisfactory[5,6], appears to be safe[5–7], and might reduce costs[8].

During the COVID-19 pandemic, the need for telemedicine options became more urgent, not only to handle high patient loads, but also to reduce the amount of contact between caregivers and contagious patients. Telemedicine-based hospital-at-home interventions to avoid admission or facilitate early discharge were implemented in multiple countries for patients with COVID-19[9–14]. Building on the success of these interventions, hospitals are now looking to continue and expand the availability of telemedicine-based hospital-at-home to a broader patient population[15]. However, the required facilities for telemedicine for COVID-19 patients are relatively simple, with oxygen therapy, dexamethasone, and vital signs monitoring being the cornerstones of therapy. The care that needs to be organized for other infectious diseases might be more elaborate, e.g. the need for intravenous antibiotics. Furthermore, not all patients appear to be suitable candidates for telemedicine-based hospital-at-home interventions[6,9,11]. Optimal patient selection is thus necessary and might improve effectiveness of hospital-at-home care.

In this study, we describe the characteristics of patients that are currently being admitted to the internal medicine ward with a suspected infection. We aimed to gain insight into the components of hospital care these patients receive, the timing of received care, and differences in received care between certain patient groups. Based on this information, we suggest a design for a telemedicine-based hospital-at-home intervention for patients suspected or diagnosed with infectious diseases.

METHODS

We conducted an exploratory, retrospective, single centre cohort study, as part of the SePsis in ACutely ill patients in the Emergency room (SPACE) study[16]. SPACE is an ongoing observational cohort study; the database includes all patients with suspected infection presenting at the emergency department (ED) of the tertiary hospital University Medical Centre Utrecht, Utrecht, the Netherlands since September 2016. Ethical review of this study was waived by the MERC Utrecht (16-594). Considering the retrospective nature and high volume of the study, individual informed consent was deemed not necessary by the institutional research board.

Study population and data collection

For this study, only patients from the SPACE cohort who were admitted in the year 2019 were included. We chose this year since it's the most recent year that is not influenced by the COVID-19 pandemic, but since it's a full year, it does include all seasonal fluctuations. Adult patients who presented at the ED for the internal medicine department (or subspecialties), who were suspected to suffer from an infection, and who were admitted to the hospital were included. Readmissions were recorded as new cases, unless the readmission occurred within 30 days, in which case only the first admission was included. Data of the included patients was collected from the electronic health record. We collected data on patient characteristics, including age, sex, and medical history. Of the ED visit and subsequent admission, we collected timestamped data on performed diagnostic tests, consultation by different specialties, treatments administered, first Modified Early Warning Scores (MEWS) at the ED, available MEWS during admission, and assistance in activities of daily living (ADL) by hospital staff. No data could be obtained for assistance in ADL at the ED, and only the MEWS at admission was known for the ED. MEWS during admission had a significant number of missing values (24.1%) which we chose not to impute, since missingness was not at random.

Assumptions

We divided each admission into four stages: the ED visit, the first 24 h of admission, between 24 and 72 h of admission, and the remainder of the admission. These stages were chosen since they represent important moments at which remote hospital care could be initiated: directly following ED presentation, after 24 h of admission when hospital care has been initiated, or after 72 h of hospital treatment when it is expected that the initiated therapy will have shown effect. Furthermore, in consultation with the 'hospital-at-home' program manager of the hospital, we determined which parts of hospital care were feasible and appropriate to offer at home. Rapid response team (RRT) consultation, intensive care unit (ICU) admission, high care interventions such as surgery, electrical

cardioversion and endoscopic procedures, and oxygen therapy with flows above 5L/min were determined to be care components that can only be offered in-hospital; all other components of care that were collected could theoretically be organized at home. Since the possibilities of performing radiological imaging at the patient home vary highly among regions, we assumed that all radiologic diagnostics had to be performed in the outpatient clinic. For missing MEWS during admission, we assumed it was not above the threshold for action in the hospital's protocol, since a high MEWS is more likely to be recorded than a low MEWS.

Descriptive and statistical analysis

First, we described patient characteristics of the entire cohort during the four stages of admission. We used this information to determine whether obvious subgroups could be distinguished, e.g., based on age or admission diagnosis. Secondly, we calculated the percentage of patients who received a certain component of hospital care during a specific stage of hospital admission, both for the entire cohort and for the admission diagnosis groups that were most common. This information was used to determine: 1. which components of hospital care were most frequent, 2. at which stage of hospital admission these components were administered, and 3. whether differences existed in the percentage of people receiving certain hospital care between subgroups. Next, for every patient we established whether they had received hospital care that can only be offered in the hospital, or not. This information was used to determine the number of patients that could theoretically be discharged after each stage (directly after ED presentation, after 24 hours, after 72 hours) to receive the remaining hospital care at home.

The total number of possible combinations of hospital care components (>150) was too high for categorization based on received care. Instead, we decided to group the components into 'packages' of hospital care that could be offered at home. The selection of these packages was based on the occurrence of the hospital care components (e.g. laboratory tests were very common, and therefore included in most packages), the ease with which a particular component could be organized at home (e.g. a patient could administer his/her own subcutaneous medication after a short training, whereas a certified nurse and equipment is needed for intravenous administration), and the need for transportation (oxygen therapy can be administered at home, radiology tests need to be performed within a care facility). Additionally, we added a package of hospital-at-home care with telemonitoring previously described by Summerfelt et al.[6]. For each care package, we determined the number of patients that could receive hospital-at-home care after each stage of admission. We selected the package that was deemed most efficient (most patients at home with least complex and least amount of care components) to

describe in more detail. As final part of the exploration, we used a multivariate binary logistic model to determine factors that predict whether a patient would be able to receive hospital-at-home care after each stage of admission. Clinically relevant variables were chosen and eliminated using backward selection. We constructed four models: one for the prediction of 'being able to go home with the selected package' at any point in time, and one going home after each stage, separately. A p-value <0.05 was considered statistically significant. All analyses were performed using SPSS version 26.0 (IBM Corp., IBM SPSS Statistics for Windows, Armonk, NY).

RESULTS

The cohort consisted of 763 admitted patients (table 1). Patients were admitted mostly to the general internal medicine ward (35%), followed by oncology (21%) and nephrology (16%). The most common admission diagnoses were lower respiratory tract infection (LRTI) (27%), urinary tract infection (UTI) (19%) and gastrointestinal infection (GI) (18%). Most frequently occurring components of hospital care were laboratory tests, intravenous/other invasive (IV) and intradermal/subcutaneous/intramuscular (ID/SC/IM) medication administration, and intercollegiate consultation (table 2). Intercollegiate consultation occurred most often with a colleague in internal medicine (12.1%), followed by geriatric medicine (10.8%), pulmonology (10.5%), cardiology (9.7%) and neurology (8.8%). The four most common components were also most common for patients with LRTI, UTI or GI. Patients with LRTI received more other components of care compared with the overall cohort. Patients with UTI more often needed a urine catheter (supplemental tables 1-3). Radiologic diagnostics, especially X-ray or ultrasound, were most commonly performed at the ED (79% of all patients) and less during admission.

Table 1. Patient characteristics.

	N=763		N=763
Age (median, IQR)	62 (47-72)	Admission specialty	
≥ 65	348 (46%)	- General Internal Medicine	263 (35%)
Female sex	360 (47%)	- Oncology	163 (21%)
CCI (median, IQR)	5 (2-7)	- Nephrology	124 (16%)
Medical history		- Haematology	112 (15%)
- Hypertension	385 (51%)	- Other	101 (13%)
- Diabetes	197 (26%)	Admission diagnosis	
- Chronic kidney disease	149 (20%)	- Lower respiratory tract infection	206 (27%)
- Haemodialysis dependent	28 (4%)	- Urinary tract infection	141 (19%)
- Metastatic malignancy	140 (18%)	- Gastrointestinal infection	134 (18%)
- Haematological malignancy	100 (13%)	- Systemic viral infection	93 (12%)
- COPD	71 (9%)	- Skin infection	56 (7%)
Presented by ambulance	147 (19%)	- Non-infectious diagnosis	50 (7%)
MEWS at presentation (median, IQR)	3 (1-5)	- Unknown	44 (6%)
Length of hospitalization (median, IQR)	4 days (2-8)	- Other	39 (5%)
ICU admission during hospitalization	86 (11%)		
Died during hospitalization	46 (6%)		

IQR: interquartile range, CCI: Charlson Comorbidity Index, MEWS: Modified Early Warning Score, ICU: intensive care unit.

Table 2. Percentage of admitted patients receiving care components during four stages of admission.

	ED N=763	<24h N=763	24h-72h N=705	>72h N=496
Diagnostics				
- lab	758 (99%)	498 (65%)	566 (80%)	405 (82%)
- X-ray/U	603 (79%)	134 (18%)	130 (18%)	170 (34%)
- CT/MRI/other	120 (16%)	95 (13%)	63 (9%)	102 (21%)
Interventions				
- Oxygen therapy 1-5L/min	123 (16%)	208 (27%)	155 (22%)	119 (24%)
- Oxygen therapy >5L/min	43 (6%)	43 (6%)	21 (3%)	28 (6%)
- ID/SC/IM medication	317 (42%)	345 (45%)	334 (47%)	265 (53%)
- IV / other hospital medication^	659 (86%)	629 (82%)	540 (77%)	322 (65%)
- Central intravenous catheter	11 (1%)	6 (0.8%)	9 (1%)	19 (4%)
- Urine catheter	28 (4%)	158 (21%)	163 (23%)	126 (25%)
- Feeding tube	3 (0.4%)	67 (9%)	72 (18%)	82 (17%)
- High care intervention^	14 (2%)	33 (4%)	31 (4%)	51 (10%)
- Intercollegiate consultation	50 (7%)	428 (56%)	420 (60%)	342 (69%)
- RRT consultation	4 (0.5%)	12 (2%)	4 (0.6%)	4 (0.8%)
- ICU admission	55 (7%)	62 (8%)	64 (9%)	44 (9%)
Patient stability and self-reliance				
- MEWS ≥ 3	ND	208 (27%)	151 (21%)	129 (26%)
- MEWS ≥ 5	ND	112 (15%)	72 (10%)	72 (15%)
- Assistance in ADL	ND	138 (18%)	148 (21%)	173 (35%)
- Physiotherapist consultation	0 (0%)	30 (4%)	122 (17%)	209 (42%)

0% of patients 100% of patients

ED: emergency department, ID: intradermal, SC: subcutaneous, IM: intramuscular, IV: intravenous/other invasive, RRT: rapid response team, MEWS: Modified Early Warning Score, ADL: Activities of Daily Living, IQR: interquartile range, ND: no data.
*Other imaging: PET/CT, lung perfusion and/or ventilation scan. ^Other hospital medication: medication administration for which additional care and/or expertise is needed, such as peritoneal or intravesicular administration, or medication via feeding tube. ^Invasive intervention: surgery, bronchoscopy, cystoscopy, endoscopy, transesophageal ultrasound, cardioversion, radiologic intervention, peripheral nerve block, and similar procedures.

Of all included patients, 133 (17%) received care that could not have been delivered at home during all periods. The remaining 630 patients could theoretically have received hospital-at-home care at some point during admission, provided that all care components can be delivered at home. A total of 562 patients (74%) could in theory have received hospital-at-home care immediately following their ED visit (figure 1). The admission specialties and diagnoses for patients in this group were the same as for the entire cohort. Median hospital length of stay (LOS) was 4 days (IQR 2-7). The most occurring components of hospital care (laboratory tests, intercollegiate consultation, IV and ID/SC/IM medication) were also the most common components in this group.

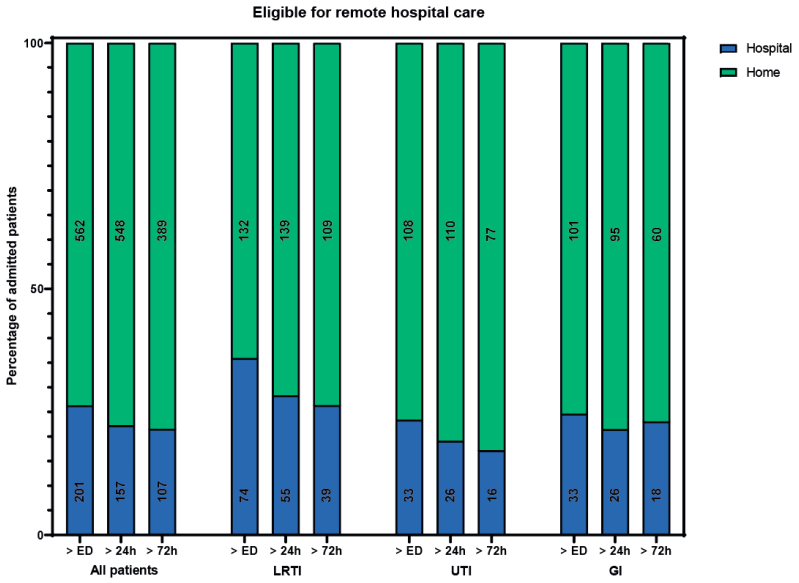

Figure 1. Percentage of patients eligible (in green) for remote hospital care if all components were available at home, besides rapid response team consultation, intensive care admission, high care intervention, or oxygen therapy >5L/min. Number of patients in a bar is presented in the bar. ED: emergency department. LRTI: lower respiratory tract infection. UTI: urinary tract infection. GI: gastrointestinal infection.

Analysis of care packages

Based on the results and complexity of different components, we composed different packages of care (table 3). Package 3 had a high number of patients that could receive care at home with relative few complex intervention components (figure 2). This package consisted of the base package plus laboratory tests, IV medication, and oxygen therapy, and the possibility to receive radiology at home or in an outpatient setting. With this package, 362 (48%) of the patients could have gone home with hospital care at some point during admission. Packages without the option for IV medication (basic package

and package 1) resulted in considerably less patients that would be eligible for hospital-at-home. Addition of ADL and physiotherapy to package 3, as described in the study by Summerfelt et al.[6] (package 4), increased the total number of eligible patients from 362 to 483 (63%). The highest number of eligible patients that could have received hospital-at-home care was found with package 5, which is the most elaborate care package.

Table 3. Care package compositions.

Package	Rationale	Care components
Basic package	Components that can always be arranged for every patient. Intradermal, subcutaneous and/or intramuscular medication administration can be taught to the patient and/or a caregiver.	• Telemonitoring and video consultation • Intercollegiate consultation • Intradermal/ subcutaneous/ intramuscular medication
1.	The most important problem is the self-sustainability of the patient. The patient cannot easily come to a clinic.	Basic package + • Laboratory tests • ADL assistance • Physiotherapy
2.	Simple diagnostics and therapy that a patient can receive without assistance. The patient is mobile and can go to an outpatient clinic for diagnostics if necessary.	Basic package + • Laboratory tests • Radiology tests • Oxygen therapy
3.	Slightly more elaborate diagnostics, a trained professional is needed for IV medication.	Package 2 + • Intravenous/other invasive medication
4. (Summerfelt)	The study by Summerfelt et al. report an existing hospital at home intervention, in which in-person visits were replaced with video consultation and telemonitoring as much as possible.	Package 3 + • ADL assistance • Physiotherapy
5.	The majority of components can be arranged at home, however with a limitation to the number of certain components, as to not overburden home healthcare professionals.	Package 4 + • Urine catheter OR central venous catheter OR feeding tube

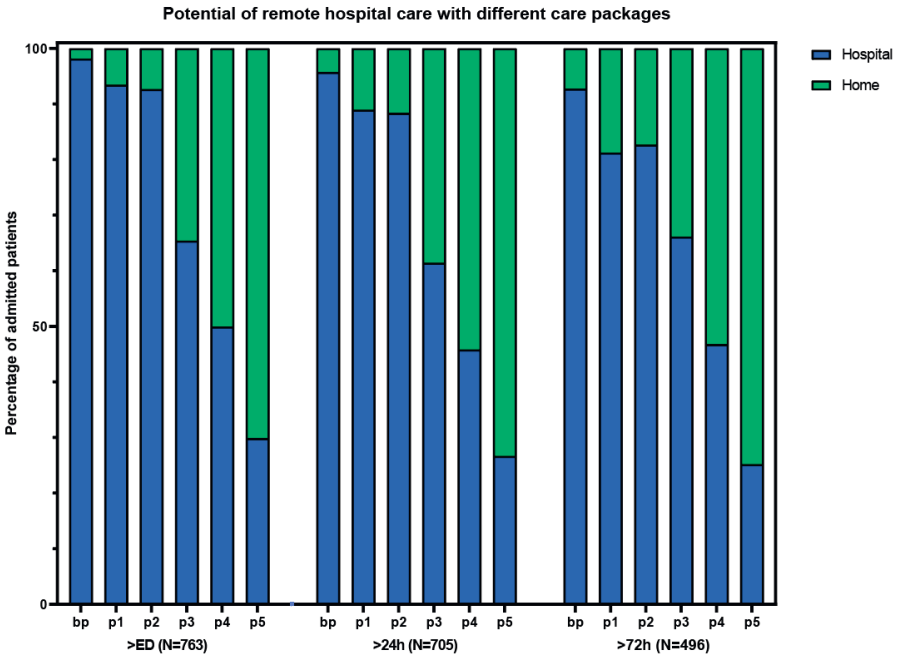

Figure 2. Potential of remote hospital care with different care packages. ED: emergency department. bp: basic package. p1: package 1 (bp + laboratory tests + ADL assistance + physiotherapy). p2: package 2 (bp + laboratory tests + radiology tests + oxygen). p3: package 3 (p2 + IV medication). p4: package 4 (p3 + ADL + physiotherapy). p5: package 5 (p4 + urine catheter OR central venous catheter OR feeding tube).

Analysis of package 3

The patients that could have received care at home with package 3 were younger (median age hospital 65 (IQR 52-74) vs. median age home 56 (IQR 42-68)), and the admission specialties and diagnoses were more diffusely divided (table 4). These patients were also less sick, with shorter length of stay and lower mortality rate. The MEWS at presentation however was comparable in both groups. Of the care components of package 3 that were needed by the at-home care group, IV medication was the most frequent within 24 hours (78%) and laboratory tests were most frequent in the following days (for 24-72h and >72h resp. 70% and 61%) (table 5). After breaking IV administration down by type of medication, we found that most patients received intravenous antibiotics. The use of radiological imaging was diffusely spread over the periods of time. CT/MRI imaging were performed most often, although absolute numbers were small.

Table 4. Characteristics of patients eligible for hospital-at-home care with package 3.

	>ED		>24h		>72h	
	Hospital (N=499)	**Home (N=264)**	**Hospital (N=433)**	**Home (N=272)**	**Hospital (N=328)**	**Home (N=168)**
Characteristics						
- Age(median, IQR)	65 (52-74)	56 (42-68)	66 (52-74)	58 (45-70)	65.5 (52-74)	61.5 (46-72)
- CCI (median, IQR)	5 (3-7)	4 (2-6)	5 (3-7)	4 (2-6)	5 (3-7)	4 (2-7)
- Admission specialty						
- General Internal Medicine	211 (42%)	59 (22%)	189 (44%)	57 (21%)	140 (43%)	41 (24%)
- Oncology	116 (23%)	47 (18%)	97 (22%)	53 (20%)	74 (23%)	29 (17%)
- Nephrology	64 (13%)	60 (23%)	56 (22%)	61 (22%)	40 (12%)	49 (29%)
- Hematology	56 (11%)	56 (21%)	45 (10%)	62 (23%)	39 (12%)	31 (19%)
- Other	52 (10%)	42 (16%)	46 (11%)	39 (14%)	35 (11%)	18 (11%)
- Admission diagnosis						
- Lower respiratory tract infection	163 (33%)	43 (16%)	142 (33%)	52 (19%)	109 (33%)	39 (23%)
- Urinary tract infection	101 (20%)	40 (15%)	87 (20%)	49 (18%)	61 (19%)	32 (19%)
- Gastrointestinal tract infection	77 (15%)	57 (22%)	63 (15%)	58 (21%)	46 (14%)	32 (19%)
- Viral infection	41 (8%)	52 (20%)	34 (8%)	47 (17%)	23 (7%)	28 (17%)
- Skin infection	31 (6%)	25 (10%)	26 (6%)	26 (10%)	21 (6%)	14 (8%)
- Other	86 (17%)	47 (18%)	81 (19%)	40 (15%)	68 (21%)	23 (14%)
- Length of hospitalization (median, IQR)	6 (4-10)	2 (2-4)	7 (4-11)	3 (2-4)	9 (6-13)	4 (4-6)
- Died (n, %)	43 (9%)	3 (1%)	36 (8%)	2 (0.7%)	2 (0.6%)	1 (0.6%)
- MEWS ≥3	167 (34%)	41 (16%)	184 (43%)	21 (78%)	118 (36%)	11 (7%)
- MEWS ≥5	100 (20%)	12 (5%)	108 (25%)	4 (2%)	69 (21%)	3 (2%)
- MEWS at presentation (median, IQR)	3 (1-5)	2 (1-4)	3 (2-5)	2 (1-4)	3 (2-5)	2 (1-4)

ED: emergency department, IQR: interquartile range, MEWS: Modified Early Warning Score.

Table 5. Percentage of patients eligible for hospital-at-home care with package 3 receiving care components.

	<24 (N=264)	24-72h (N=272)	>72h (N=168)
Diagnostics			
- Laboratory test	143 (54%)	190 (70%)	103 (61%)
- Radiological imaging	33 (13%)	29 (11%)	21 (13%)
- X-ray	6 (2%)	10 (4%)	12 (7%)
- Ultrasound	17 (6%)	8 (3%)	0 (0%)
- CT/MRI	13 (5%)	15 (6%)	8 (5%)
- Other medical imaging*	0 (0%)	0 (0%)	3 (2%)
- Intercollegiate consultation	115 (44%)	114 (42%)	72 (43%)
Interventions			
- Oxygen therapy 1-5L/min	32 (12%)	20 (7%)	7 (4%)
- ID/SC/IM medication	88 (33%)	92 (34%)	58 (35%)
- IV/other hospital medication^	205 (78%)	189 (70%)	82 (49%)
- Resuscitation fluid	12 (5%)	9 (3%)	7 (4%)
- Blood products	1 (0.4%)	1 (0.4%)	1 (0.6%)
- Antibiotics	166 (63%)	162 (60%)	65 (39%)
- Else	85 (32%)	74 (27%)	37 (22%)

0% of patients 100% of patients

ID: intradermal, SC: subcutaneous, IM: intramuscular, IV: intravenous.
*Other imaging: PET/CT, lung perfusion and/or ventilation scan. ^Other hospital medication: medication administration for which additional care and/or expertise is needed, such as peritoneal or intravesicular administration, or medication via feeding tube.

Identification of eligibility factors for package 3

Older age, higher MEWS, arriving by ambulance, and admission to a general internal medicine ward decreased the likelihood of being eligible for remote hospital care with package 3 at any point in time (supplemental table 4). For hospital-at-home care directly after ED visit, being diagnosed with a lower respiratory tract infection also decreased the chance of being eligible. These factors did not impact eligibility for remote hospital care after 72 hours. At this point in time, the chances of being eligible were higher for patients admitted for the nephrology department, and patients with skin or viral infections. However, confidence intervals for these groups were wide, since only few patients had one of these diagnoses.

DISCUSSION

In this study, we explored which components of care are needed for a telemedicine-based hospital-at-home intervention for patients with infectious diseases. We found that the potential for hospital-at-home is high, and for one in three patients it might already be possible directly after ED visit. An intervention consisting of telemonitoring, virtual consultations, laboratory and radiologic diagnostics, medication, and oxygen therapy could potentially allow hospital-at-home care to almost half of our study population.

Selection of care components

The four components of hospital care in our study that were most frequently administered in all patient groups and time periods were ID/SC/IM medication, IV/other invasive medication, laboratory testing, and intercollegiate consultation. These are components that have been frequently organised in previous hospital-at-home interventions too[17–21]. Components such as a urine catheter, central venous catheter, or feeding tube have been less frequently used previously. These care components require regular episodes of professional nursing care, and are often a sign of more severe illness. Since oxygen therapy at home can easily be used by patients with relatively little guidance, we have added this component to the majority of care packages. Assistance in ADL is a common component of other hospital-at-home interventions; however, we have purposely left this out of the majority of packages, since assistance in ADL is one of the factors that makes hospital-at-home labour intensive[22]. Although vital instability was uncommon among patients eligible for hospital care at home, a MEWS of 3 or higher still occurred, which is associated with a 12.7% chance of ICU admission[23]. Telemonitoring of vital signs therefore needs to be a basic component of virtual hospital care at home to allow early recognition of patient deterioration that may necessitate hospital readmission. Regardless of the theoretical simplicity of organizing care components at home, it is important to keep in mind the reason why patients require certain care. The underlying disease, or especially uncertainty about the underlying disease, might be a reason to opt for hospitalization instead of hospital-at-home care on itself.

Timing of care

We found that a substantial number of patients was potentially eligible for hospital-at-home care immediately after the ED visit. This type of hospital-at-home care is called ‘avoided admission’, as opposed to early ‘supported discharge’. Avoided admission by hospital-at- home care has shown to provide benefits in clinical outcomes and costs[3]. Arranging the logistics however is more challenging, since all care needs to be organized during the relatively short ED visit. Admission avoidance hospital-at-home care could even be taken further, by not sending the patient to the ED at all[24]. However, the majority of

patients in our study received care at the ED, especially diagnostics – including imaging studies - and IV medication. A hospital-at-home intervention which also aims to avoids the ED visit will have to include a 'fast track' organization of these components at home, or at a minimum, the possibility to perform these at a primary care facility.

Patient selection

Although hospital-at-home care is desirable especially for elderly patients[4], higher age was associated with less eligibility for hospital-at-home care with the selected package in our study. Elderly patients need more care, specifically care components that require frequent home visits such as ADL assistance. If the goal is to provide hospital-at-home care for elderly patients, home visits should not be avoided. Nonetheless, reasons for participating in hospital-at-home care might be even more patient-specific than what we could investigate in this study. The availability and capacity of a supporting caregiver, the home situation, and the patient's self-sufficiency have shown to be important factors in patient eligibility[25]. For hospital-at-home care supported by telemedicine specifically, the ability of a patient to work with telemonitoring and video consultation devices is crucial. It also requires more of a patient's self-sufficiency than in-person hospital-at-home, since many tasks will shift from the nurses' responsibility to the patient's responsibility. Furthermore, a subset of eligible patients will refuse hospital-at-home care, mainly because they prefer to receive care within the hospital, or have concerns about the safety of hospital-at-home care[20,26]. Since we have not measured these components in our study, the ultimate number of hospital-at-home patients will likely be smaller than the theoretical numbers as reported in this study.

Cost considerations

Although the use of telemedicine reduced the number of home visits, it does not necessarily reduce costs. A recent study on the use of telemonitoring for early discharge of surgical patients found that the intervention was only cost-effective if implemented on all hospital wards, even without extra interventions such as diagnostics or medicinal treatment at home[8]. The reason for this is the high costs for purchase and maintenance of technology, and the requirement for 24/7 availability of staff. This intervention did not offer care at home besides monitoring and video consultation. Adding care components will increase costs, but also increase the number of eligible patients. Moreover, valuable components including home visits are required to provide care for specific target populations, such as frail elderly or patients that need frequent clinical evaluation. The goal should therefore not be to avoid costly components, but to design the most efficient intervention. The organization of individual care components should also be taken into account. For example, radiological imaging to diagnose pneumonia could be performed in three ways. The patient could be brought to the hospital by ambulance for a chest

X-ray, which will cost €760 for ambulance transport in the Netherlands[8]. The patient could also be brought by a family member, or a taxi service, which costs significantly less. The hospital could also equip a professional with a portable ultrasound device and let the professional visit the patient to image the lungs, which is a valid alternative[27]. This will cost €130 per visit[8], plus any costs for the purchase and maintenance of the device. An ultrasound probe might even be sent to the patient, who then makes the images him/herself -guided by an expert over videoconferencing- and send the images to the hospital, eliminating the need for the imaging visit altogether[28]. As seen in this example, the costs for hospital-at-home with telemonitoring are not easily calculated and will depend to a large extent on organisational choices.

Strengths and limitations

In this study we structurally investigated what types of care are administered during hospitalisation, and to determine which of these might be offered at home. This is a first step towards hospital-at-home care based on the needs of the patient, rather than on what the hospital can offer. We used a large cohort, representative of a complete year of admissions for various infectious diseases, and took various aspects of hospital care into consideration. Throughout the study we have made decisions driven by data, without losing sight of clinical relevance. This study also has several limitations. Due to the retrospective nature of the study, the decision making process by hospital professionals that resulted in the patient being admitted was hard to determine. We might have missed components of care that always require hospital admission, which might have led to an overestimation of the proportion of patients with infectious disease who are eligible for hospital-at-home care. Although we tried to take frailty of patients into account, by including care components such as physiotherapy consultation and ADL assistance, this is not equivalent to a formal frailty screening. Secondly, the study was conducted in a tertiary centre with an accompanying specific patient population, and only for those patients who presented with a suspected infection. Conclusions can therefore only be generalized to similar populations. Some interventions to limit hospital admission were already in place during this study. For oncology patients for example, the MASCC risk index[29] has been used since 2014 to determine whether a patient should be admitted with intravenous antibiotics or can be discharged with an oral variant, resulting in a preselected population. Lastly, we assumed that every part of care a patient received during admission was strictly necessary, which might not always be true. Previous studies showed that patients at home with hospital care typically receive less interventions than hospitalised patients, with similar patient outcomes[30,31]. In-hospital overutilization of care components such as laboratory tests is well known[32]. Received care in the hospital might therefore not necessarily reflect needed care at home. These limitations might have resulted in an underestimation of the population eligible for hospital-at-home care.

Future perspectives

This study was limited by its retrospective design. In a prospective design, four questions in particular that would be interesting to investigate: 1. What care do patients receive that are not recorded in the EPD? 2. What part of the provided care is not strictly necessary and could be omitted? 3. What are reasons for hospital professionals to admit, or not yet discharge, a patient? 4. Of all patients that are theoretically eligible for hospital-at-home care, which patients are not able to, or do not wish to participate and why? Answering these questions will further complete our understanding of the potential and optimal design of a hospital-at-home care intervention for this population. Furthermore, a prospective study of the proposed intervention with care package 3 should be performed to test the feasibility, to verify the number of patients that are eligible for intervention, and to find components of care that are missing in this intervention. In this stage, all stakeholders should be involved, including patients, care at home providers, and general practitioners.

CONCLUSION

For patients currently admitted with a suspected infection, the potential for virtual hospital-at-home care is high. The proportion of eligible patients depends to large extent on the required care components in the home setting. With a combination of telemonitoring and video consultation, laboratory and radiologic diagnostics, medication, and oxygen therapy, hospital-at-home care could potentially be offered to almost half of our population with suspected or proven infection.

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SUPPLEMENTAL MATERIAL

Supplemental table 1. Percentage of admitted patients receiving care components during four periods of admission for patients with lower respiratory tract infections.

	ED N=206	<24h N=206	24h-72h N=194	>72h N=148
Diagnostics				
- lab	206 (100%)	137 (67%)	158 (81%)	119 (80%)
- X-ray/U	197 (96%)	41 (20%)	45 (23%)	61 (41%)
- CT/MRI/other*	35 (17%)	93 (45%)	15 (8%)	32 (22%)
Interventions				
- Oxygen therapy 1-5L/min	68 (33%)	108 (52%)	87 (45%)	59 (40%)
- Oxygen therapy >5L/min	23 (11%)	29 (14%)	16 (8%)	15 (10%)
- ID/SC/IM medication	93 (45%)	98 (48%)	93 (48%)	80 (54%)
- IV / other hospital medication^	183 (89%)	181 (88%)	140 (72%)	87 (59%)
- Central intravenous catheter	5 (3%)	1 (0.5%)	2 (1%)	4 (3%)
- Urine catheter	8 (4%)	49 (24%)	50 (26%)	40 (27%)
- Feeding tube	1 (0.5%)	29 (14%)	31 (16%)	29 (20%)
- High care intervention†	3 (2%)	8 (4%)	2 (1%)	10 (7%)
- Intercollegiate consultation	15 (7%)	116 (56%)	126 (65%)	112 (76%)
- RRT consultation	3 (2%)	6 (3%)	4 (2%)	2 (1%)
- ICU admission	21 (10%)	27 (13%)	27 (14%)	20 (14%)
Patient stability and self-reliance				
- MEWS ≥ 3	ND	89 (43%)	70 (36%)	54 (37%)
- MEWS ≥ 5	ND	57 (28%)	33 (17%)	35 (24%)
- Assistance in ADL	ND	44 (21%)	48 (25%)	61 (41%)
- Physiotherapist consultation	0 (0%)	12 (6%)	52 (27%)	84 (57%)

0% of patients 100% of patients

ED: emergency department, ID: intradermal, SC: subcutaneous, IM: intramuscular, IV: intravenous/other invasive, RRT: rapid response team, MEWS: Modified Early Warning Score, ADL: Activities of Daily Living, IQR: interquartile range, ND: no data.
*Other imaging: PET/CT, lung perfusion and/or ventilation scan. ^Other hospital medication: medication administration for which additional care and/or expertise is needed, such as peritoneal or intravesicular administration, or medication via feeding tube. †High care intervention: surgery, bronchoscopy, cystoscopy, endoscopy, transesophageal ultrasound, cardioversion, radiologic intervention, peripheral nerve block, and similar procedures.

Supplemental table 2. Percentage of admitted patients receiving care components during four periods of admission for patients with urinary tract infections.

	ED N=141	<24h N=141	24h-72h N=136	>72h N=93
Diagnostics				
- lab	140 (99%)	96 (68%)	116 (85%)	76 (82%)
- X-ray/U	107 (76%)	23 (16%)	21 (15%)	26 (28%)
- CT/MRI/other*	15 (11%)	15 (11%)	13 (10%)	12 (13%)
Interventions				
- Oxygen therapy 1-5L/min	19 (14%)	28 (20%)	21 (15%)	14 (15%)
- Oxygen therapy >5L/min	9 (6%)	5 (4%)	0 (0%)	2 (2%)
- ID/SC/IM medication	62 (44%)	70 (50%)	69 (51%)	51 (55%)
- IV / other hospital medication^	129 (92%)	122 (87%)	115 (85%)	59 (63%)
- Central intravenous catheter	3 (2%)	0 (0%)	1 (0.7%)	2 (2%)
- Urine catheter	11 (8%)	45 (32%)	50 (37%)	37 (40%)
- Feeding tube	1 (0.7%)	6 (4%)	5 (4%)	6 (7%)
- High care intervention†	5 (4%)	6 (4%)	7 (5%)	8 (9%)
- Intercollegiate consultation	5 (4%)	77 (55%)	73 (54%)	57 (61%)
- RRT consultation	0 (0%)	2 (1%)	0 (0%)	1 (1%)
- ICU admission	11 (8%)	12 (9%)	11 (8%)	7 (8%)
Patient stability and self-reliance				
- MEWS ≥ 3	ND	34 (24%)	23 (17%)	22 (24%)
- MEWS ≥ 5	ND	17 (12%)	10 (7%)	8 (9%)
- Assistance in ADL	ND	29 (21%)	33 (24%)	29 (31%)
- Physiotherapist consultation	0 (0%)	4 (3%)	27 (20%)	31 (33%)

0% of patients 100% of patients

ED: emergency department, ID: intradermal, SC: subcutaneous, IM: intramuscular, IV: intravenous/other invasive, RRT: rapid response team, MEWS: Modified Early Warning Score, ADL: Activities of Daily Living, IQR: interquartile range, ND: no data.

*Other imaging: PET/CT, lung perfusion and/or ventilation scan. ^Other hospital medication: medication administration for which additional care and/or expertise is needed, such as peritoneal or intravesicular administration, or medication via feeding tube. †High care intervention: surgery, bronchoscopy, cystoscopy, endoscopy, transesophageal ultrasound, cardioversion, radiologic intervention, peripheral nerve block, and similar procedures.

Supplemental table 3. Percentage of admitted patients receiving care components during four periods of admission for patients with gastrointestinal infections.

	ED N=134	<24h N=134	24h-72h N=121	>72h N=78
Diagnostics				
- lab	134 (100%)	98 (73%)	93 (77%)	66 (85%)
- X-ray/U	75 (56%)	26 (19%)	12 (10%)	20 (26%)
- CT/MRI/other*	28 (21%)	15 (11%)	10 (8%)	15 (19%)
Interventions				
- Oxygen therapy 1-5L/min	10 (8%)	19 (14%)	15 (12%)	15 (19%)
- Oxygen therapy >5L/min	3 (2%)	3 (2%)	2 (2%)	4 (5%)
- ID/SC/IM medication	55 (41%)	62 (46%)	60 (50%)	44 (56%)
- IV / other hospital medication^	112 (84%)	101 (75%)	86 (71%)	59 (76%)
- Central intravenous catheter	1 (0.7%)	2 (2%)	1 (0.8%)	3 (40%)
- Urine catheter	2 (2%)	24 (18%)	17 (14%)	12 (15%)
- Feeding tube	1 (0.7%)	6 (5%)	13 (11%)	14 (18%)
- High care intervention†	1 (0.7%)	12 (9%)	9 (7%)	13 (17%)
- Intercollegiate consultation	11 (8%)	77 (58%)	67 (55%)	54 (69%)
- RRT consultation	0 (0%)	2 (2%)	0 (0%)	1 (1%)
- ICU admission	6 (5%)	7 (5%)	7 (6%)	4 (5%)
Patient stability and self-reliance				
- MEWS ≥ 3	ND	56 (19%)	17 (14%)	15 (19%)
- MEWS ≥ 5	ND	12 (9%)	10 (8%)	10 (13%)
- Assistance in ADL	ND	27 (20%)	20 (17%)	28 (36%)
- Physiotherapist consultation	0 (0%)	4 (3%)	11 (9%)	23 (30%)

0% of patients 100% of patients

ED: emergency department, ID: intradermal, SC: subcutaneous, IM: intramuscular, IV: intravenous/other invasive, RRT: rapid response team, MEWS: Modified Early Warning Score, ADL: Activities of Daily Living, IQR: interquartile range, ND: no data.

*Other imaging: PET/CT, lung perfusion and/or ventilation scan. ^Other hospital medication: medication administration for which additional care and/or expertise is needed, such as peritoneal or intravesicular administration, or medication via feeding tube. †High care intervention: surgery, bronchoscopy, cystoscopy, endoscopy, transesophageal ultrasound, cardioversion, radiologic intervention, peripheral nerve block, and similar procedures.

Supplemental table 4. Prediction of eligibility for hospital-at-home care with package 3.

		>any point		>ED		>24h		>72h	
		OR	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**
Age		**0.99**	**0.98-1.00**	**0.98**	**0.97-0.99**	**0.99**	**0.98-0.99**	-	
MEWS at ED		**0.91**	**0.84-0.98**	**0.88**	**0.81-0.95**	**0.90**	**0.83-0.98**	0.93	0.84-1.02
Brought in by ambulance		**0.50**	**0.32-0.78**	**0.41**	**0.24-0.70**	**0.44**	**0.26-0.73**	-	
Admission specialty*	General Internal Medicine	**0.46**	**0.28-0.78**	**0.50**	**0.29-0.86**	**0.45**	**0.26-0.78**	0.62	0.31-1.24
	Oncology	0.67	0.39-1.15	0.58	0.33-1.02	0.69	0.39-1.22	0.78	0.38-1.63
	Nephrology	1.44	0.80-2.61	1.34	0.74-2.44	1.24	0.68-2.28	**2.60**	**1.22-5.52**
	Hematology	1.18	0.65-2.15	1.37	0.75-2.51	1.72	0.93-3.20	1.42	0.65-3.07
Admission diagnosis^	LRTI	0.81	0.39-1.71	**0.41**	**0.19-0.89**	0.61	0.27-1.35	2.42	0.64-9.01
	UTI	0.82	0.38-1.77	0.48	0.21-1.07	0.71	0.35-1.84	2.38	0.62-9.24
	GI	1.29	0.60-2.78	0.75	0.34-1.64	0.61	0.27-1.35	3.68	0.94-14.4
	Skin infection	1.80	0.75-4.32	1.10	0.45-2.68	1.69	0.66-4.31	**4.88**	**1.13-21.1**
	Viral infection	2.19	0.97-4.94	1.25	0.55-2.82	1.45	0.61-3.43	**6.07**	**1.50-24.6**
	Other diagnosis	0.84	0.38-1.88	0.53	0.23-1.23	0.50	0.21-1.20	2.55	0.64-10.2

OR: odds ratio, CI: confidence interval, ED: emergency department, MEWS: Modified Early Warning Score, LRTI: lower respiratory tract infection, UTI: urinary tract infection, GI: gastrointestinal infection.

*Reference category: other specialties. ^Reference category: unknown diagnosis.

CHAPTER 8

General Discussion

Technology is a rich source for new vital signs monitoring possibilities. But if the technology and its effect on the existing workflow are not sufficiently understood, implementation might not lead to the desired outcomes. Before implementing new monitoring techniques on a large scale, we should determine the optimal design for the intervention. Assumptions that were made during the design should be thoroughly assessed, since they might not hold true in clinical practice. And finally, the effect of the intervention should be measured, not only on patient outcome, but on all stakeholders involved. In this chapter, I discuss the current evidence, the evidence added by the studies in this thesis, and highlight current gaps in knowledge, of both in-hospital continuous monitoring and remote monitoring at home. I will end with future perspectives on the implications of modern monitoring methods on health care organisation, including recommendations for future research on this subject.

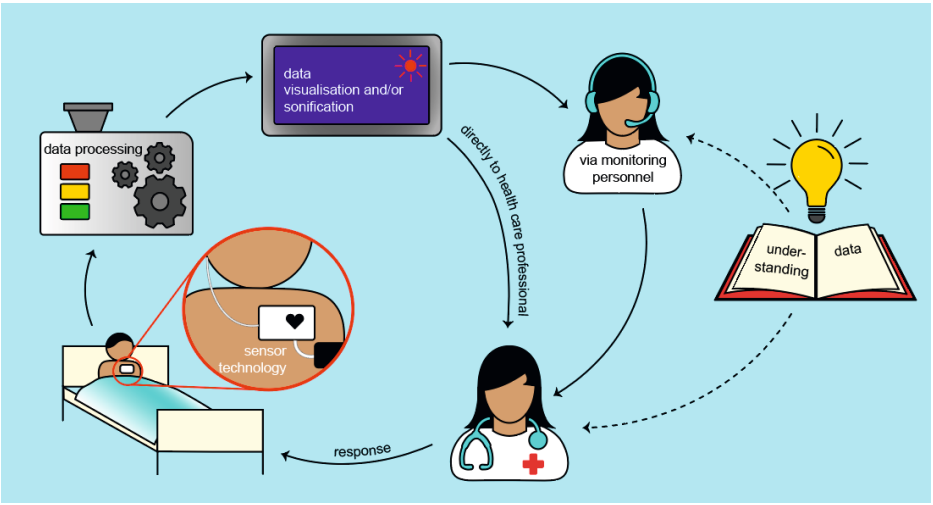

Figure 1. Components of a monitoring wearable wireless monitoring strategy.

CONTINUOUS MONITORING

Although multiple studies have reported on the validity and feasibility of sensor technology for continuous monitoring of hospitalised patients[1], there is currently little evidence that it improves clinical outcomes[2]. One explanation for this might be the complexity of a monitoring strategy consisting of many components, of which sensor technology is only the first[3] (figure 1). First, all measurements need to be displayed in a certain way, either with or without being processed first, and with or without an alarm strategy. This display could be visible for a variety of health care professionals, who need to have sufficient

knowledge of the system and the interpretation of vitals sign trends to correctly interpret the displayed data. In case of home monitoring, the patients themselves are also a likely link in this system. Finally, there needs to be an adequate response to abnormal data patterns in order for the monitoring to have any effect on clinical outcome at all.

Which sensor to use

Most studies on continuous monitoring have covered the validity of sensor measurements. Measurements from wearable sensors were often outside acceptable limits for one or more parameters[1]. The type of sensor will therefore likely be an important factor in the success of the intervention. Fortunately, stricter rules for medical devices and validation protocols[4,5] are already in place to improve the quality of wearable sensors. A second decision that has to be made regarding sensors is which vital signs to monitor. This seems to be a matter of 'which vital signs are needed to detect deterioration'. The effect on the workplace, however, also needs to be taken into consideration. 'Complete' multi-parameter sensors that are able to measure all vital signs, might take more work off the hands of nurses than sensors that measure only a few select vital signs. Such a 'complete' multi-parameter sensor would make manual measurements redundant, creating more time for nurses to do other important tasks[6]. However, many current wearables cannot or do not provide the full set of vital signs. In particular, measurement of blood oxygen saturation and blood pressure are technically challenging. Hospital professionals and patients voiced concerns that limited necessity for nurses to enter a patient's room to take vital signs could decrease important bedside interaction with the patient[7,8]. In Chapter 5 we report that the introduction of a system for (almost) complete continuous monitoring did not result in a decrease in patient room visits by nurses. One of the explanations could be that not all vital signs can currently be monitored wirelessly; to our knowledge, no reliable wireless continuous core temperature or consciousness sensor is currently in use in-hospital. For these measurements, patient visits are still required. More importantly, taking vital signs is only one of many nurse-patient interactions[7], which takes up less time than other patient care activities[9]. At least in theory, nurses would have more time for other important activities, such as talking with and observing the patient, when reliable automated vital sign measurements are available [10]. It is important to realise that if continuous monitoring is pursued to reduce the number of nurses, quality of care and outcome are likely to suffer. Continuous monitoring is an aid, and not a replacement, for nursing care.

'Intelligent' technology?

Wearable sensors are often called 'smart'. However, marketing tends to exaggerate the true intelligence of sensor technology. Intelligence is "the ability to learn, understand and think in a logical way about things"[11]. Current systems simply record and report vital signs as they are designed to do, without critical evaluation. The logical thinking and

understanding has to come from the people working with the technology. For example, in case of an alarm for missing heart rate measurements in a previously stable patient, it is up to humans to determine whether the change is harmless (the sensor has come loose) or serious (the patient is in asystole). Similarly, one cannot expect technology to perform tasks it is not programmed for. A model trained to detect trends in heart rate over hours, will not be able to detect asystole within seconds. Monitoring technology can be made 'smarter' by using additional measurements and algorithms to improve signal quality and discard unreliable measurements. Accelerometers for example could help distinguish between movement artefacts and physiological abnormalities[12], and measuring impedance can determine if the electrode is still attached to the skin. Moreover, prediction models could be used to generate real-time alerts on (pending) vital instability. The current prediction models in use for continuous monitoring are mostly based on a version of the 'early warning score', a composite score developed for intermittent manual patient monitoring[13–15]. The advantage of this approach is that multiple vital parameters can be combined into one score, which can be easily communicated by nurses and physicians. The disadvantage is that very little of the information stored in continuously measured vital signs data is actually used to make a prediction. Several alterations could be made to improve the prediction of deterioration based on continuous data, which I will discuss hereafter.

a. Feature selection

First, a prediction model for continuous monitoring data would likely take trends of individual and combined vital signs into account instead of isolated measurements, since trends have shown to have added value in intermittently measured vital signs[16]. Ongoing studies are attempting to use changes in vital signs and trend indicators to make better predictions, i.a. using machine learning[17,18]. Which features should be used in such a model however remains uncertain. In Chapter 3, we explored several methods to summarise continuously measured vital signs data, to make it suitable for use in prediction models. We showed that the association of summary measures with the endpoint respiratory insufficiency in COVID-19 patients depends on the vital sign and the selected timeframe. This evaluation could be used as the starting point to select the optimal features for (machine-learned) algorithms. Features that are not previously discussed, but have potential to be of added value in prediction models, are derivatives of classic vital signs such as heart rate variability or pulse pressure[17,19].

b. Time-related considerations

Additional choices are introduced by the extra dimension of continuously measured vital signs: time. Summary measures need to be calculated over a pre-determined period of data, the timeframe, in order to be able to use them in a prediction model. As mentioned

and shown in Chapter 3, the length of this timeframe influences the strength of the association of a summary measure with the endpoint. Timeframes of 4 hours appear to have stronger associations than 8-hour timeframes for most summary measures, but the optimal length of a timeframe is yet unknown. Longer timeframes, e.g. 24 hours, contain more trend information. However, it will take at least 24 hours before the first prediction can be made, which is clinically undesirable. Alternatively, very short timeframes of, e.g., 10 min are highly influenced by circumstances such as movement, and might therefore be less informative outside of high-care settings, especially if the model is not informed on activity. The optimal timeframe length will likely be somewhere in between these extremes, or a combination of the two. Two different predictions could be made, one over a short (e.g. past hour) an one over e long (e.g. past 12 hours) timeframe, since both provide different clinical information (figure 2.a and 2.b). Long and short timeframes could also be combined into one prediction. For example, data could be divided into short timeframes, and summary measures over these timeframes are combined to make one prediction, in which summary measures are weighted depending on how far in the past a timeframe is (figure 2.c). Beside the timeframe length, the prediction frequency needs to be determined. A new prediction could be made with the start of each new timeframe (e.g., with timeframes of 2 hours, every 2 hour a prediction is made) (figure 2.c), but timeframes could also overlap to make predictions more frequently (e.g. every hour a prediction is made with the previous 2 hours of data) (figure 2.d). This will determine the frequency with which hospital professionals are provided with updated information. Lastly, the length of the prediction window needs to be chosen. This is the amount of time between the prediction and the occurrence of the endpoint that is being predicted. Timeframe length, prediction frequency and prediction window will likely be determined by what is clinically most needed, and might differ between wards, diseases, patient groups, or phase of hospitalisation.

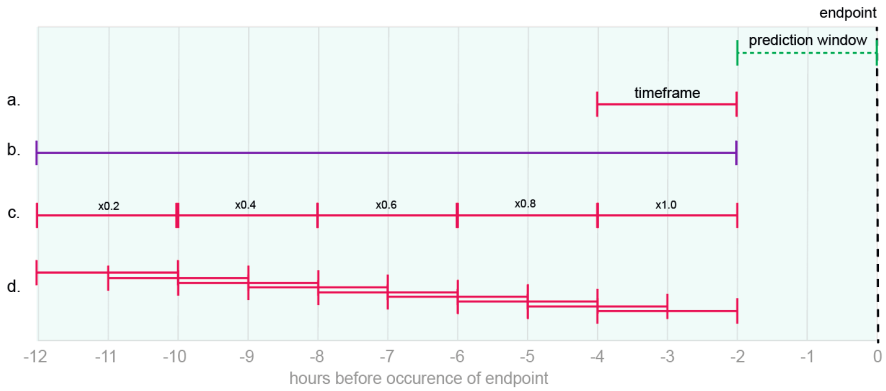

Figure 2. Different methods to select continuously measured data, by using a. short timeframes, b. long timeframes, c. multiple weighted timeframes, d. rolling timeframes/moving window.

c. Endpoint selection

Most current prediction models for patient deterioration predict ICU admission, cardiac arrest and/or death[20]. Alternative endpoints however might better reflect clinical need. For example, in case of COVID-19, hospital professionals indicated that respiratory insufficiency was clinically the most relevant to predict, which is why we chose this endpoint in Chapter 3. Prediction models could be designed to predict specific adverse events, e.g., complications that often occur or that are easily missed, or they could help recognise the need for certain time-critical interventions[21]. Data could also be used to predict the trajectory of vital signs, if no action would be undertaken to change this trajectory[22]. The choice of endpoint should reflect a clinical need, which will be further discussed in the section *Impact on clinical workflow.*

d. Circadian rhythm

Another aspect of continuously measured vital signs data is described in Chapter 2: the circadian rhythm. A circadian rhythm is the rhythmic pattern of measurements over a 24 h cycle, which is caused by biological and environmental factors, sleep, and exercise[23]. In Chapter 2 we were able to show that a circadian pattern can be observed in respiratory rate, heart rate and skin temperature of COVID-19 patients. Part of the variation we see in continuously measured vital signs data can be explained by this circadian rhythm, but could be mistaken for deterioration. The physiological rise in respiratory rate and heart rate in the morning, for example, could lead to an inappropriate deterioration alarm. By accounting for this circadian rhythm, prediction models will be able to make more accurate predictions. An example is given by van Rossum et al.[24], who showed that using different alarm thresholds during day and night improves alarm performance, when combined with other adaptive threshold-based strategies.

e. Additional data

To create the 'ultimate' prediction model for clinical deterioration, other data than vital signs may need to be added. To predict imminent respiratory failure in COVID-19, adding the amount of administered oxygen as a possible predictor could be helpful[25]. Baseline information, such as age, comorbidities, medication use, and type of disease, are likely to contribute to performance of the model, since they can have a direct effect on the underlying physiological processes of which vital signs are indicators. Information on activity, e.g., whether a patient is currently talking, walking, or sleeping, could be used to improve a prediction algorithm in two ways. First, different values for vital signs are expected during activity than during rest. Correcting for movement in an algorithm might improve its predictive value. Secondly, the physical activity level of a patient, in itself, might also yield valuable prognostic information, since critically ill patients are expected to be less physically active, while delirious patients can be hyperactive. Another

addition could be intermittently measured data such as laboratory results, which have also shown to add to prediction scores[26–29]. Nevertheless, if a parameter is only intermittently measured, its addition should be carefully weighted, since it automatically introduces one of two limitations: 1. it either limits the update frequency of the model to the measurement frequency of the non-continuous parameter, or 2. it introduces missing values during periods of time during which the non-continuous parameter is not measured.

f. Model development

Considering the high number of features and complex mechanisms that we would like a prediction model for continuous monitoring data to take into account, an artificial intelligence-based model might be better suited for data processing than a traditional (regression-based) model. Furthermore, an artificial intelligence-based model can be designed to keep learning while being implemented. This creates the opportunity to make models that are tailored for specific wards or specific patient groups. Machine learning also has several downsides. One important downside is the 'black box' phenomenon, where the model makes a prediction, but hospital professionals does not understand what the prediction is based on, making them less likely to accept and use the model[30]. A traditional regression model is more transparent and more easily understood by professionals, but is also less able to process big data and find complex patterns. The development of any prediction model, using either traditional regression techniques or machine learning, depends on the availability and quality of needed data. Standardised collection and sharing of data in repositories could accelerate the creation of adequately sized data bases, and thus the development of the optimal prediction model.

As shown in this paragraph, much work has yet to be done to develop a prediction model that can make optimal use of the properties of continuously measured vital signs data, and make technology truly smarter. Fortunately, another source of intelligence is widely available on hospital wards that we can use to detect patient deterioration: human intelligence.

Interpretation by hospital professionals

Chapter 4 provides some insight into the factors that caregivers weigh to make a decision regarding the vital status of a patient. It shows that many factors that we would like the 'ultimate prediction model' to take into account, such as time of day or patient characteristics, are already routinely considered by hospital professionals. However, this chapter also highlights the existence of considerable variability between hospital professionals when interpreting vital sign trends: without prior training or protocols, there is very little consensus whether a particular vital signs trend from a COVID-19

patient indicates deterioration. Training and support are needed to get everyone on the same page, and there are multiple ways to do so. This could be as simple as implementing an early warning score specifically designed for continuously measured vital signs data instead of intermittently measured values. Summary measures as suggested in Chapter 3 for example could be used to create such a prognostic score (figure 3).

Figure 3. Fictive prognostic score using summary measures of continuously measured data.

Compare 4 hours of data with previous 4 hours of data. Give points for change in:					
Points	-2	-1	0	1	2
Mean respiratory rate	≥5/min ↓	2-4/min ↓	1/min ↓ – 1/min ↑	2-4/min ↑	≥5/min ↑
Mean heart rate	≥10/min ↓	4-9/min ↓	3/min ↓ – 3/min ↑	4-9/min ↑	≥10/min ↑
Number of desaturations <90%	≥5/hour ↓	2-4/hour ↓	1/hour ↓ – 1/hour ↑	2-4/hour ↑	≥5/hour ↑

More elaborate decision support systems are also imaginable, in which an algorithm as described previously is used to alert hospital professionals to changes that otherwise might have been missed. This could be done by using alarms. One of the perils of adding alarms is alarm fatigue. If too many alarms are non-actionable, hospital professionals will get desensitised, which leads to not recognising or not reacting to real deterioration[31]. Also, in one study nurses indicated to find alarms unnecessary when they have received sufficient training and a protocol for documentation in place[13]. If a useful decision support system is to be implemented, with a reasonable number of actionable alarms, hospital professionals should be involved in the creation of the system to determine the right source data, endpoint, outcome measure, interpretation and presentation[32]. The goal of the decision support system might differ depending on the type of ward, type of patient, and perhaps also time of day. In previous studies, nurses have indicated to see the added value especially during night shifts[6,33], for two reasons: 1. the nurse-to-patient ratio is lower and therefore more patients are not seen for longer periods of time, leading to a higher possibility of missed deterioration, and 2. for very good reasons nurses are reluctant to wake a sleeping patient to routinely check vital signs. In this example, a bespoke support system could be developed that is focussed on detecting deterioration during the night.

It is important to emphasize that vital signs, or any other measurements used in a prediction model, are not the only indicator of how a patient is doing. Hospital professionals' direct patient observation and especially 'nurse worry' are important early

indicators of deterioration[34]. As seen in Chapter 4, many hospital professionals indicate that they need to see their patient, in order to make an accurate estimation of his/her condition, especially when it comes to possible deterioration. The computability of this 'gut feeling' is limited[32]. Ideally, continuous monitoring of vital signs should not be an alternative for, but an adjunct to, bedside assessment of a patient's vital stability.

Impact on clinical workflow

As described in the section *Which sensor to use*, the choice of sensor technology could impact the workflow of hospital professionals through the requirement for additional measurements. But this is only one of the ways continuous monitoring of vital signs might change the current workflow. For example, the battery life also impacts the amount of time a nurse invests in vital sign measurements. If time is gained by introducing a 'complete' multisensor (eliminating the time needed for manual measurements), but the battery of this device needs to be replaced every shift, ultimately no 'time spent on measuring vital signs' is regained. The time spent on a certain task by hospital professionals is affected by several more factors: 1. the device to access data, 2. the presentation of data on the screen (including those of mobile devices), 3. the way of visualisation or sonification of alarms, 4. integration into the electronic health record, 5. the protocolled frequency of data assessment and of patient assessment, 6. the introduction of a dedicated monitor or not, and 7. the agreed way to communicate aberrations. The complexity of the intervention makes it hard to determine which aspects specifically need to be studied, and some aspects only become apparent during or after implementation. Process evaluation during the implementation of continuous monitoring could a useful way to uncover effects on clinical workflow without having to trial every assumption made[35].

Some effects of continuous monitoring on the way we use vital signs might be more subtle than measurable in hours or in patient room visits. With intermittent monitoring, vital signs are often used to confirm or quantify a suspicion of deterioration, whereas the first clue of deterioration is given by physical clues of the patient[36]. If continuous monitoring is used, the vital signs data is more readily available than physical evaluation of the patient. The vital signs data now becomes the starting point of the evaluation, and aberrations seen in vital signs data lead to a bedside patient evaluation. In Chapter 4, hospital professionals often indicated that the first thing they would do when deviations in continuous vital signs data are observed, is visit the patient. Hospital professionals will now go to a patient with a reason, and not because the protocol dictates they must take vital signs. In Chapter 5 the number of patient room visits did not decrease after implementation of continuous monitoring, but it is plausible that the visits were made more purposefully. Furthermore, vital signs data are a quantifiable source of information. Quantifiable information can be more easily used and is more convincing when used

to communicate deterioration between nurses and physicians[13,37]. The real-time availability of (quantifiable) vital signs data might therefore help and empower hospital professionals to escalate care if needed[13,37].

Since continuous monitoring should be an adjunct to bedside assessment of a patient's vital stability, the continuous monitoring system should smoothly coincide with the needs and way of the people in the workplace. If continuous monitoring feels like a nuisance or increases workload, hospital professionals will neither support the implementation and nor will they engage with it[38]. The eventual aim of continuous monitoring is to help care professionals detect deterioration of patients at the ward, and the intervention should be designed with this aim in mind. For prediction models, this means including them in the design of the prediction model. A prediction model will not work, if it does not predict an outcome that is of importance to hospital professionals, does not assist the decision making process, or does not render an actionable alarm[39]. Therefore, we should ask hospital professionals which endpoint they want to see predicted, where in the workflow the model should intervene, and what alarms are useful for them to act on[32]. The practical application of monitoring, too, should meet the needs of the workplace. For example, having to use different software than the hospital EHR for presenting continuous monitoring data is not only annoying, because hospital professionals will have to open this software separately to be able to see measurements[6], it could create unsafe situations resulting from missed patient deterioration. Instead of simply giving nurses accounts to new software, software producers and EHR vendors should collaborate to integrate continuous measurements into the existing systems. This does not necessarily mean that every measurement should be uploaded into the EHR, which would clutter the patient records. Leenen et al., for example, had physicians evaluate monitoring data once a day, and nurses twice per shift, and document findings in the EHR[13]. This matched the existing workflow of regular vital sign assessment and was considered satisfactory by hospital professionals and led to timely recognition of deteriorating patients.

A factor not to be forgotten is the actionability of presented data. So far, we have focussed mainly on obtaining measurements and interpreting their meaning. However, no patient was ever rescued by measurements alone. The second ('efferent') part of rapid response systems is timely remedial action, and in case of severely aberrant vital signs the deployment of a rapid response team[40] to help assess and stabilise the patient. A future challenge will be to design appropriate protocols for how to act on deviations observed in continuously measured vital signs data, whether noted by a hospital professional or detected by an algorithm. Proper execution of his step will prove invaluable to ultimately be able to observe a positive effect on patient outcomes.

MONITORING OUTSIDE THE HOSPITAL WALLS

Hospitals are now actively searching for ways to provide the same standard of care at home as in the hospital[41,42]. So-called 'hospital-at-home' care has the potential to improve patient well-being[43], decrease the number of hospital admission-related adverse events, and preserve hospital beds for those who need them[44]. Since monitoring of vital signs and evaluation of disease progression is an essential part of hospital care, it is also one of the cornerstones of remote hospital care. Hospital-at-home care, however, is an even more complex intervention, and the assumptions should be thoroughly assessed.

Design and target population

Chapter 6 shows that a randomised trial of remote hospital care for COVID-19 patients leads to different conclusions than retrospective studies[45–47]. One of these conclusions is that a subset of patients is unwilling to go home with hospital-at-home care. This has been observed previously in other hospital-at-home studies[48,49]. The reason is often two-sided: patients do not trust that hospital-at-home care will be safe, or they just rather be in the hospital during recovery[48]. Safety concerns are likely to decrease as hospital-at-home care becomes more common. We should also increase the patient's readiness to go home by providing better guidance, communication, and shared decision making throughout care transitions[50]. The second conclusion is that a considerable proportion of patients is not suited for hospital-at-home care. This was also observed in other hospital-at-home interventions[46,51]. Reasons for this are the need for care that can only be offered in-hospital, no suitable home situation, or not being self-sufficient enough for hospital-at-home care. Although frail elderly patients are a typical group for which we would prefer to avoid hospitalisation when possible[52], we found that they are often the least eligible for hospital-at-home care, since they more often require components of care that cannot yet be arranged at home (Chapter 7). Furthermore, this is also the patient population with less health literacy, including limited skills to use digital tools, which has to be considered when offering hospital-at-home care virtually. Although these skills can be taught, a period of acute illness is not the ideal situation to do so. When designing a hospital-at-home care intervention, we might have to distinguish between patients who are self-reliant on one hand, and who could be cared for at home with mostly remote modalities, as proposed in package 3 of Chapter 7. On the other hand, we might want to design an intervention which is focussed on avoiding hospitalisation of frail or elderly adults, which will be more elaborate and include more in-person care and daily assistance[53].

Effectiveness and costs

Another conclusion from the randomised trial discussed in Chapter 6 concerns the difference in length of hospitalisation. During the trial, it proved difficult for clinicians to correctly estimate the remaining duration of hospitalisation. Consequently, patients who were expected to remain in the hospital for several more days, sometimes recovered more quickly than expected, and were discharged the next day instead. This might be one of the reasons why the difference in hospital admission between intervention and control group was smaller than estimated in retrospective studies[45–47]. This might also partly explain why 'admission avoidance' hospital-at-home care interventions have resulted in more beneficial effects on clinical outcomes and costs[44]; admission avoidance always reduces the number of hospitalised days, while early discharge does not always do so. For future hospital-at-home care interventions, the timing of the intervention should therefore be as soon as organisation-wise possible. Fortunately, in Chapter 7 we see that hospital-at-home care is already possible for a large group of internal medicine patients with infectious diseases immediately following the ED visit. But even if virtual hospital-at-home care could be arranged for a large group of patients, it might not result in major cost reduction. A study in a surgical population shows that the large investment needed for technical implementation and the costs for 24/7 availability of monitoring personnel often outweigh the savings from shorter hospitalisation, especially if the intervention is implemented on a smaller scale[54]. The authors of this study therefore state that virtual hospital-at-home care should probably be seen as an affordable way to handle the increasing demand for care, instead of a way to reduce costs[54].

Future perspectives and opportunities for further research

In 2011, the Royal Dutch Medical Association (Koninklijke Nederlandsche Maatschappij tot bevordering der Geneeskunst, KNMG) released an international report regarding the future directions of medical specialties in 7 developed countries. They state that current health care systems will not be sustainable in the future. To face the changing population and community needs, health care organization will become more community-based and less hospital-based. Patients will have an increased role and responsibility for care[55]. In the report 'The role of the physician' in 2022, they emphasise that future care will be centred around the patient, both physically and virtually[56].

As the patient becomes the centre of health care organisation, the difference between 'inpatient' and 'outpatient' will further dissolve. The decision to hospitalise will no longer be based on the available facilities in the hospital, but on the needs of the patient. The default location for care should therefore be the community. Only those requiring care that cannot be arranged at home, or those with a home situation that is not suited for

care at home, will be hospitalised. Several qestions that need to be answered before this can be organised:

1. **Which care exactly do patients need?**
2. **Which care elements can only be provided in the hospital?**
3. **Can we find acceptable at-home alternatives for care components that are currently only offered in-hospital?**

This shift from hospital-centred care to patient-centred care also involves a shift of care responsibility. Patients will not only be more involved in the decision-making process, but also in the practical execution of care. Moreover, with the pressing issue of increasing hospital staff shortages[57] more patient involvement is needed for sustainable healthcare. This also leads to important research questions:

4. **What can, and what cannot, be considered the patient's responsibility?**
5. **How can we optimise patient involvement in execution of care?**

Even the distinction between 'patients' and 'people' is vanishing as technology evolves. During the SARS-CoV-2 pandemic, it became clear that every person is a potential patient, and that tracking down disease before it becomes symptomatic can be an effective tool to prevent spread of disease. Although consumer wearables are not medical grade devices, and the validity, safety and use are therefore not as strictly regulated, data generated by consumer wearables can aid the timely detection of disease. Researchers showed that vital signs data obtained by smartwatches can be used to detect or predict COVID-19[58,59], just as previous research has shown that smartwatches can aid in detecting atrial fibrillation[60]. A paper in 2020 reports a man who detected his ST-elevation myocardial infarction using the single-lead ECG of his smartphone[61]. This too is in line with the developments of health care organization to preventing disease and improving population health[56]. Modern vital sign technology will eventually play a role in primary care, emergency care, hospital- and recovery care. Future research should also aim to:

6. **Determine how consumer-electronics vital signs technology can aid in the prevention and detection of disease and timely recognition of deterioration in the general population.**

Wearable monitoring has not only made its introduction for people in the community, but several hospitals have started to use continuous monitoring of vital signs for patients at home too[62–65]. Continuous monitoring at home poses a new set of challenges. Since direct patient observation is limited, it is more difficult to decide what to do with

ambiguous deviations, or if a patient should be called and woken up in case of signal loss. Lessons learned from implementation of in-hospital continuous monitoring could help solve these problems. Technology that is easy to wear and is least sensitive to motion artefact will results in less missing data, which could avoid the need to call and wake a patient at night. New algorithms that reliably recognize and ignore artefacts, and produce only the most useful alarms, could prevent alarm fatigue for both personnel remotely monitoring patients at home and the patients themselves. Use of accelerometers and measuring impedance might help distinguish between a cardiac arrest and a loose ECG electrode. Ultimately, the same technology could be used both in and outside the hospital, diminishing the difference between in-patient and out-patient care even further. Clinical research should keep up with these developments, and place the focus of research beyond simply assessing the validity of sensor measurements[66]. This includes the aim to:

7. **Find the most efficient way to process continuously measured vital signs data.**
8. **If alarms are to be part of this strategy, find a way to generate only the most useful alarms.**

Since big data storage will be needed to achieve this aim, health care institutions will also have to carefully consider

9. **How to organise storage, standards, security, ethics, data rights, and governance**[66].

With those patients who are able to be cared for at home staying at home, the patients who do require hospitalisation will have a higher burden of care than the current hospital population. These patients will likely benefit most from continuous monitoring of vital signs, since the risk of deterioration is higher. Increased knowledge of how to use and interpret continuously measured vital signs is needed to best support hospital professionals in their care for hospitalised patients. Therefore, we need to

10. **Determine which features of continuously measured vital signs best indicate the need for a clinical evaluation.**
11. **Design a protocol on how to evaluate and react to findings in continuous monitoring data.**

The critical scientific evaluation of modern monitoring techniques is of utmost importance to prevent the introduction of ineffective interventions. Unfortunately, the traditional ways of evaluating effectiveness, with the randomised controlled trial as the ultimate tool, is not always suited for digital health interventions[67,68]. The added value of these interventions can only be measured when the optimal design is found and has

become part of standard care. This is problematic, since we aim to only implement care that is already evidence-based. In the developmental phase of (digital) interventions, those in charge of deciding whether an intervention is implemented or not should be open to evidence created by alternative designs that might better match these interventions. In these designs, development and implementation are a simultaneous and continuous process[67,68]. Nonetheless, it is important that the added value can eventually be reported.

CONCLUSION

Technological innovation of monitoring methods has caused a shift away from manual intermittent vital signs measurements by nurses, to continuous, remote measurements by wearable sensors. The evolving field of monitoring research is slowly uncovering the implications of this paradigm shift on patient outcomes and care organisation. Despite some promising local implementations, much work is yet to be done to optimise monitoring strategies and remote care interventions. Organizations should be careful not to implement new technologies without understanding, or at least assessing, the impact on all stakeholders and processes involved. Researchers should aim to provide the best scientific evidence to help determine which technology to implement, what it can and cannot do, and how it can aid in providing the right care at the right place. Ultimately, continuous and remote monitoring will help bring the patient to the centre of health care organisation.

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Samenvatting
Curriculum Vitae
Dankwoord

SAMENVATTING

De hoofdstukken van dit proefschrift beschrijven diverse aspecten en klinische uitdagingen van continue monitoring van vitale parameters op afstand. Het eerste hoofdstuk geeft hierop een introductie. Hoofdstukken 2 en 3 beschrijven aspecten van het gebruik van continue gemeten vitale parameters. Het vierde en vijfde hoofdstuk gaan in op het gebruik van continue monitoring op een verpleegafdeling voor patiënten met COVID-19. Hoofdstukken 6 en 7 bevatten interventies waarin monitoring op afstand gebruikt wordt om ziekenhuiszorg thuis mogelijk te maken. Het laatste hoofdstuk bediscussieert alle voorgaande hoofdstukken, inclusief een visie voor de toekomst.

In **hoofdstuk 1** wordt beschreven waarom het meten van vitale functies wordt gedaan, en hoe de meetmethoden over de tijd zijn veranderd. Vitale parameters zijn numerieke metingen van essentiële lichaamsfuncties, en geven een indicatie van de gezondheid en stabiliteit van de patiënt. Het meten van vitale parameters is onder andere beïnvloed door beschikbare technologie, de documentatie van metingen, en het toenemend besef van het belang van vitale functies om achteruitgang van een patiënt vroegtijdig te kunnen herkennen. Dit besef groeide nadat werd vastgesteld dat in het geval van bij deze patiënten in de 8 uur voorafgaand al sprake was van afwijkende vitale parameters. In eerste instantie werd daarom de Early Warning Score geïntroduceerd, een geaggregeerde score van onder andere diverse vitale parameters die tenminste eens per 8 uur wordt afgenomen om de vitale status van een patiënt in kaart te brengen. Om echter geen enkele afwijking te missen, is de afgelopen jaren ook technologie geïntroduceerd die vitale functies continu en op afstand kan meten. Met name tijdens de COVID-19 pandemie, welke begon in 2020, leek dit een zeer waardevolle manier van meten en monitoren. Echter, het onderzoek naar een aantal facetten van deze innovatieve meetmethode is nog beperkt. De impact van deze complexe interventie op patiëntuitkomsten is onzeker, en over andere uitkomsten zoals ziekenhuisorganisatie is nog weinig bekend. Dit proefschrift gaat in op een aantal bevindingen en uitdagingen wanneer continue monitoring en monitoring op afstand in de praktijk worden toegepast.

In **hoofdstuk 2** beschrijven we een circadiaan ritme in hartritme, ademhalingsfrequentie en huidtemperatuur van COVID-19 patiënten die opgenomen zijn in het ziekenhuis. Vitale functies volgen fysiologisch gezien een dag-nacht ritme. In de literatuur is gesuggereerd dat ziekte-ernst dit ritme zou kunnen beïnvloeden. Het bestaan van een circadiaan ritme in continue monitoringsdata is potentieel van invloed op hoe deze data geïnterpreteerd moet worden. In een retrospectieve studie vonden wij inderdaad circadiane variaties in hartfrequentie, ademfrequentie en huidtemperatuur bij herstellende COVID-19 patiënten. Bij COVID-19 patiënten die respiratoir insufficiënt werden of overleden werd het ritme

aangetoond voor hartfrequentie, maar niet voor ademfrequentie of huidtemperatuur. Ondanks dat er verschillen werden gevonden tussen patiënten die respiratoir insufficiënt werden of overleden en patiënten die herstelden, konden we geen duidelijk patroon in circadiaan ritme vinden dat achteruitgang van de patiënt zou kunnen voorspellen. Verandering in het circadiaan ritme van patiënten lijkt dus geen predictieve waarde te hebben voor het voorspellen van klinische achteruitgang.

Hoofdstuk 3 verdiept het voorspellen van respiratoire insufficiëntie van COVID-19 patiënten op basis van continu gemeten vitale parameters. Om continue monitoringsdata zinvol te kunnen kwantificeren is een manier nodig om de grote hoeveelheid data samen te vatten. In dit hoofdstuk onderzochten we verschillende manieren om hartfrequentie-, ademfrequentie- en saturatiebeloop samen te vatten, en in hoeverre deze samenvattingsmaten geassocieerd zijn met het ontwikkelen van respiratoire insufficiëntie bij opgenomen COVID-19 patiënten. We vonden dat samenvattingsmaten die berekend waren over een periode van 4 uur over het algemeen een sterkere associatie lieten zien dan wanneer ze werden berekend over 8 uur. Verder laten samenvattingsmaten meestal een sterkere associatie zien wanneer de gemeten tijdsperiode dichterbij het tijdstip van het eindpunt is. Het gemiddelde liet een sterke associatie zien met respiratoire insufficiëntie in alle gemeten parameters, voor alle getoetste tijdsperiodes. De sterkte van associatie van overige samenvattingsmaten verschilde per parameter, maar was ook afhankelijk van de gekozen tijdsduur waarover de samenvattingsmaat was gemeten, en hoe lang voor respiratoire insufficiëntie dit gemeten was. Bij het ontwikkelen van een klinische score of een voorspellend algoritme is het dus belangrijk met deze factoren rekening te houden.

Continue monitoring heeft niet alleen effect op de patiënt, maar ook op de zorgverleners die met de techniek moeten werken. Omdat het voor veel zorgverlener buiten de intensieve zorg units een nieuwe methode is, weten we nog niet goed hoe zorgverleners met continue monitoringsdata omgaan. In **hoofdstuk 4** hebben we daarom 24 zorgverleners verschillende casus van COVID-19 patiënten laten beoordelen, op basis van het beloop van continu gemeten vitale parameters, en gevraagd of ze vinden dat de patiënt stabiel is, verbeterd of verslechterd. Hieruit blijkt dat zij, zonder ervaring of training, niet tot dezelfde conclusies komen. Uit interviews komen hiervoor mogelijke oorzaken naar voren. Ten eerste blijken zorgverleners verschillende strategieën voor beoordeling te gebruiken: op basis van drempelwaardes, op basis van trends, of een combinatie van beiden. Hierbij zijn ze met name op zoek naar afwijkingen in de data. Er zijn echter nog geen goede handvatten om de bevindingen en afwijkingen te kwantificeren. Daarnaast geven zorgverleners aan dat het moeilijk is om iets over de patiënt te zeggen zonder de patiënt zelf te kunnen zien. Onderzoek en een protocol naar welke kwantitatieve maten voor

continue data behulpzaam zijn bij beoordelen zouden kunnen helpen om de interpretatie van continue data te verbeteren en te harmoniseren. Ook bleek uit deze studies dat zorgverleners het zelden mis hebben als ze denken dat een patiënt respiratoir insufficiënt wordt, maar wel moeite hebben om sommige casus van respiratoire insufficiëntie te herkennen. Een alarmerings- of beslissingsondersteunend systeem zou kunnen helpen om ook deze patiënten te detecteren.

Een van de mogelijke nadelen die genoemd wordt van continue monitoring is dat zorgverleners hierdoor mogelijk minder vaak naar de patiënt toe zouden gaan. Bij patiënten in isolatie, zoals COVID-19 patiënten, zou dit juist weer een voordeel kunnen zijn, omdat het aantal potentiële besmettingsmomenten daarmee zou afnemen. Om te toetsen of continue monitoring inderdaad een effect heeft op het aantal patiëntkamerbezoeken hebben we een voor-na studie gedaan, die beschreven wordt in **hoofdstuk 5**. In deze studie is gemeten hoe vaak artsen en verpleegkundigen de kamer van een COVID-19 patiënt bezoeken voor de invoering van continue monitoring, en erna. De resultaten geven aan dat het invoeren van continue monitoring geen effect heeft gehad op het totale aantal bezoeken of het aantal bezoeken specifiek voor het beoordelen van vitale parameters. Wel zou het kunnen zijn dat er minder 'standaard' controles werden gedaan en meer controles naar aanleiding van de metingen zelf, maar dat kan op basis van deze studie niet worden gezegd.

Tijdens de COVID-19 pandemie werd monitoring op afstand ook ingezet om patiënten thuis te kunnen behandelen in plaats van in het ziekenhuis. De patiënt kan zo in eigen vertrouwde omgeving herstellen, en in het ziekenhuis zouden dan minder (besmettelijke) patiënten liggen. Om de effectiviteit van deze interventie te meten, hebben wij een gerandomiseerde trial uitgevoerd die wordt beschreven in **hoofdstuk 6**. In deze trial werden patiënten gerandomiseerd naar de interventiegroep of de controlegroep. In de interventiegroep werd, zodra de patiënt 3L zuurstoftherapie of minder aan zuurstoftherapie nodig had, het 'naar huis' traject ingezet. Hierbij werd er zuurstof thuis georganiseerd, en werd de patiënt aangemeld voor het medisch regiecentrum, vanuit waar driemaal daags de klachten, temperatuur en saturatie op afstand werden gecontroleerd en elke dag telefonisch contact werd gezocht met de patiënt. De controlegroep kreeg reguliere ziekenhuiszorg. Hoewel de patiënten in de interventiegroep 1.6 dagen eerder naar huis gingen, resulteerde dit niet in meer dagen thuis binnen de 30 dagen na randomisatie. Daarnaast viel op dat maar een klein deel van de patiëntpopulatie (ongeveer 10%) mee wilde of kon doen aan de interventie. De effectiviteit van deze interventie lijkt daardoor minder groot dan van tevoren verwacht.

In **hoofdstuk 7** diepen we virtuele ziekenhuiszorg thuis verder uit, maar dan voor patiënten van de interne geneeskunde met andere infecties dan COVID-19. Dit onderzoek had als doel meer inzicht te krijgen in hoe een dergelijke interventie eruit zou moeten zien, en voor hoeveel patiënten dit een optie zou kunnen zijn. Hiervoor beschreven we de ziekenhuiszorg die geleverd is aan alle patiënten met een verdenking infectie die in 2019 waren opgenomen op de afdeling interne geneeskunde. Uit deze cohortstudie bleek dat de meest geleverde componenten van ziekenhuiszorg waren: laboratoriumdiagnostiek, niet-orale medicatietoediening, en intercollegiaal overleg. Op basis van de frequentie van geleverde zorg en het gemak waarmee het thuis geleverd zou kunnen worden, deden we verschillende voorstellen voor mogelijke interventies. Het pragmatisch preferente voorstel lijkt een combinatie van telemonitoring, videoconsultatie, niet-orale medicatie toediening, laboratoriumdiagnostiek, zuurstoftoediening, en de mogelijkheid tot het doen van radiologische diagnostiek. Met deze interventie zou 48% van onze patiëntpopulatie ziekenhuiszorg thuis kunnen krijgen, en voor 35% zou dat al kunnen direct na bezoek aan de spoedeisende hulp. Het potentieel lijkt dus hoog. Dit aantal is in de praktijk waarschijnlijk lager, omdat niet alle patiënten ziekenhuiszorg thuis willen of kunnen ontvangen, zoals gezien in hoofdstuk 6.

Overdenkingen op basis van de studies in dit proefschrift en suggesties voor toekomstige studies en interventies worden bediscussieerd in **hoofdstuk 8**. Belangrijke punten die naar voren komen met betrekking tot continue monitoring zijn: 1). Aspecten van data waar een voorspellend algoritme rekening mee zou moeten houden. 2). Manieren om het gebruik door zorgverleners te kunnen verbeteren. 3). Hoe continue monitoring in het dagelijks werk op de afdeling geïntegreerd kan worden. Over ziekenhuiszorg thuis met monitoring op afstand worden de volgende punten besproken: 1). De selectie van de juiste patiëntpopulatie. 2). Het aanbieden van de juiste interventie voor de juiste patiëntpopulatie. 3). Overwegingen met betrekken tot effectiviteit en kosten. Daarnaast wordt besproken welke belangrijke onderzoeksvragen in de toekomst nog beantwoord zullen moeten worden. Uiteindelijk kunnen moderne meetmethoden voor vitale functies helpen om de patiënt nog verder naar het middelpunt van de zorg te brengen.

DANKWOORD

Tijdens mijn assistentschap op de IC in Ede werd ik geconfronteerd met instabiele patiënten waarbij het gevoel heerste: “Hadden we dit niet kunnen zien aankomen?” Helaas blijft dit vaak bij frustraties. Ik prijs mijzelf gelukkig dat ik de kans heb gekregen om mee te denken over een oplossing.

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CURRICULUM VITAE – HARRIËT VAN GOOR

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Dumbledore: "*I think if you so desired, you'd be able to board a train.*"

Harry: "*And where would it take me?*"

Dumbledore: "*On.*"