Trajectories of Key Physiological Parameters in COVID-19 Patients Using Continuous Remote Monitoring and Health AI

Arik Eisenkraft (✉ aizenkra@gmail.com)

Institute for Research in Military Medicine, The Hebrew University Faculty of Medicine, Jerusalem, Israel, and the Israel Defense Force Medical Corps <https://orcid.org/0000-0002-9368-3490>

Yasmin Maor

Wolfson Medical Center, Holon, and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Keren Constantini

Department of Epidemiology and Preventive Medicine, School of Public Health, Sackler Faculty of Medicine and Sylvan Adams Sports Institute, Tel Aviv University, Tel Aviv, Israel

Nir Goldstein

Tel Aviv University <https://orcid.org/0000-0002-9271-0565>

Dean Nachman

Institute for Research in Military Medicine, The Hebrew University Faculty of Medicine, Jerusalem, Israel, and the Israel Defense Force Medical Corps

Ran Levy

Maccabi Healthcare Services, Israel

Michael Halberthal

Rambam Health Care Campus, Haifa, Israel and the Bruce Rappaport faculty of medicine, Technion, Haifa, Israel

Netanel Horowitz

Rambam Health Care Campus, Haifa, Israel and the Bruce Rappaport faculty of medicine, Technion, Haifa, Israel

Ron Golan

The Baruch Padeh Medical Center Poriya, The Faculty of Medicine in Galilee, Bar Ilan University, Israel

Elli Rosenberg

The Soroka University Medical Center, Ben-Gurion University of the Negev, Be'er Sheva, Israel

Eitan Lavon

The Kaplan Medical Center, The Hebrew University Faculty of Medicine, Jerusalem, Israel

Ornit Cohen

Wolfson Medical Center, Holon, and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Guy Shapira

Tel Aviv University, Tel Aviv, Israel. <https://orcid.org/0000-0001-9376-4955>

Noam Shomron

Tel Aviv University

Arik Ben Ishay

Biobeat Technologies LTD.

Efrat Sand

Biobeat Technologies LTD.

Roei Merin

Biobeat Technologies LTD.

Meir Fons

Biobeat Technologies LTD.

Romi Littman

Biobeat Technologies LTD.

Yftach Gepner

Tel Aviv University

Article

Keywords: COVID-19, cardiopulmonary parameters, high risk population, remote patient monitoring, artificial intelligence

Posted Date: December 15th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-122775/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Coronavirus disease 2019 (COVID-19) exerts deleterious effects on the cardiorespiratory system, leading to worse prognosis in the most affected. The aim of this retrospective multi-center study was to describe the variability of key cardiopulmonary vitals amongst hospitalized COVID-19 patients, measured every 15 minutes using a novel wearable chest-monitor. A total of 492 patients were included, with >3 million measurements collected including heart rate, systolic and diastolic blood pressure, cardiac output, cardiac index, systemic vascular resistance, respiratory rate, blood oxygen saturation, and body temperature. We show differential trajectories of these vital signs, apparent within the first 24hrs of monitoring. Importantly, we show for the first time that cardiovascular deterioration appears early after admission and in parallel with changes in the respiratory parameters, and identify sub-populations at high risk. Combining frequent monitoring using wearable technology with advanced big data and AI analysis tools may aid early detection of deterioration of COVID-19 patients.

Introduction

Several months after declaring coronavirus disease 2019 (COVID-19) a global pandemic, millions became infected all over the world, with over a million deaths due to the virus and numbers still rising. Covid-19 is a multi-system disease with a wide range of clinical manifestations, from asymptomatic patients, through simple influenza-like illness, and all the way to a fulminant disease comprised of severe respiratory involvement with acute respiratory distress syndrome (ARDS) and pulmonary insufficiency¹. As the understanding of the disease evolved, it was shown that COVID-19 damages epithelial and endothelial cells in numerous tissues leading to SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2)-related multi-organ failure¹⁻⁵. Additional damages caused by SARS-CoV-2 may include neurological diseases and hypercoagulable state⁶⁻⁸.

Previous studies have demonstrated substantial damage to the cardiovascular system with systemic hemodynamic and direct cardiac effects of the virus, a negative prognostic sign leading to myocardial injury and increased morbidity in individuals with underlying cardiovascular diseases^{1,9-23}. Respiratory parameters such as respiratory rate (RR) and blood oxygen saturation (SpO₂) are key measurements in the assessment and the prognosis of COVID-19 patients²⁴. So far, emphasis was given to infrequent spot measurements, mainly due to capabilities of currently-used devices.

Under the burden of this pandemic, resources are limited and the fear of infection transmission is high. Novel technologies may expand the capacity to remotely monitor patients, providing optimized support and protection both for COVID-19 patients and for health care providers by reducing direct contact without compromising the treatment given to isolated patients, as well as lightening the strain on the medical teams and providing early detection of patient deterioration^{25,26}. Continuous monitoring of multiple vital physiological parameters may allow better care for patients who are acutely ill, for hospital-at-home of stable patients, and for early discharge of admitted patients^{25,27}. It is also accepted that such a system would be of benefit if it frequently and automatically measures numerous vital signs, improves patient surveillance and, ultimately, improves patient outcomes^{26,28-30}. While standard vital sign measurement is executed over a single short time period and might miss crucial changes in physiological parameters, frequent remote patient monitoring (RPM) systems are potentially better equipped to detect and alert of changes since the vital signs measurements are taken continuously and for longer periods^{26,31,32}.

Several reports so far have identified differences in COVID-19 infection rates, symptom severity and mortality between sex, age, and body mass index (BMI) categories³³⁻⁴⁰; however, whether the physiological response of key cardiovascular and respiratory parameters during the course of hospitalization is different between individuals remains unknown. This knowledge may help in further understanding the clinical course of the disease and preventing clinical deterioration, with highlighted importance due to the rapid deterioration often seen in COVID-19 patients¹.

The aim of this retrospective multi-center study was to determine the trajectory of nine key and advanced physiological parameters amongst COVID-19 patients admitted to isolation units in Israeli medical centers. These parameters were continuously collected using a wearable, non-invasive, wireless chest-monitor (Biobeat Technologies Ltd., Petah Tikva, Israel; **Figure 1**), and big data analysis was conducted using advanced AI and bioinformatic tools. A special emphasis was given to characterizing the disease progression among these patients, and the identification of differences in physiological responses over time of sub-groups according to age, sex, and BMI.

Results

Initially, 571 patients participated in the study. Subjects with less than 24hrs of continuous tracking data were excluded, with 492 patients remaining in the final analysis. As can be seen in **Figure 2 a-c**, the number of patients decreased throughout the monitoring period due to patients' discharge from the hospital, transfer to intensive care units (ICU), or death. As a result, we have decided to focus our analysis on the first five days (120hrs) after admission. Physiological measurements were recorded continuously every 15 minutes with a total of 3,215,334 measurements. For the raw, unfiltered data, measurements were collected during an average monitoring period of 75.26hrs (range 0-455), with 245.67 ± 226.39 observations ($\pm$ standard deviation) per patient. The analyzed filtered data included patients with at least 24hrs of tracking, and included observations from the first five days only. Measurements were collected during an average monitoring period of 74.78hrs (range 24-120) per patient (174.89 ± 110.58).

Analysis of baseline parameters

Subject characteristics, along with mean values during the first 2hrs of monitoring (average of 8 measurements) for body temperature, SpO₂, RR, heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), cardiac output (CO), cardiac index (CI), and systemic vascular resistance (SVR) for each sub-group are presented in **Table 1**. The first 2hrs served as a baseline monitoring period for each subject. Men (64% of the recruited patients) had a significantly higher BMI and weighed more than women ($p < 0.001$). Middle aged patients (men = 70%) had significantly higher weight ($p < 0.001$) than young (men = 64%), elderly (men = 66%) and >80-year-old (men = 44%) patients, and no differences in weight were detected between the three other age groups. Young patients had significantly ($p < 0.01$) lower BMI compared to the other groups, and no differences were noted between middle age, elderly, and >80-year-old patients. Patients with normal BMI (men = 56%) were significantly ($p < 0.01$) younger.

For baseline physiological measurements, an ANOVA analysis revealed a significant ($p < 0.01$) difference between men and women for body temperature, SpO₂, HR, DBP and CO. When analyzing age groups, significant ($p < 0.003$) interactions were seen for all physiological measures recorded during the first 2hrs of admission. Lastly, only SpO₂, RR, CO and CI were significantly ($p < 0.01$) different between BMI groups upon admission.

Trajectory of physiological vitals over five days from admission

Figure 3 provides an overall description of the nine vital signs in the 130 patients that fully completed five days of continuous monitoring. Overall, within the first 24hrs we found a significant increase in temperature, RR, and SVR, and a significant decrease in SpO₂, DBP, CO and CI ($p < 0.01$ for all). These changes all appeared at the same time. For HR, SBP, CO and CI, the changes appeared in a repetitive pattern.

Further analysis is provided in **Figure 4**, where we show the results of repeated measures ANOVA tests performed to determine differences between groups during the same timeframe.

Body temperature (Figure 4a): In both males and females, temperature increased during the first 24hrs of monitoring, significantly higher among males ($p < 0.001$). From the second day, females showed a significant decrease in temperature until the fifth day ($p < 0.001$), while males' trajectory of temperature remained similar. Across the BMI groups, temperature increased similarly during the first 48hrs. A slight increase was noted in the normal weight group and decrease among the overweight and obese, but by the fifth day there were no differences within the BMI group. In the age group, temperature among the elderly was higher ($p < 0.001$) during the whole 5 days.

SpO₂ (Figure 4b): SpO₂ decreased in both males and females during the first 48hrs ($p < 0.001$ for both), with a higher decrease among males. Starting from 72hrs since admission, and throughout the next two days, females showed a quicker return to the baseline levels, while males remained with lower values ($p < 0.03$ between sex). Among the BMI sub-groups, similar trajectories were found, with higher SpO₂ levels in the normal weight sub-group, a lesser level in the overweight, and the lowest SpO₂ levels among the obese. In the age group, the young maintained SpO₂ levels throughout the five days of hospitalization with a slight reduction ($p = 0.044$), while other sub-groups showed dynamic changes with lower SpO₂ values.

Respiratory rate (Figure 4c): Within the first 48hrs from admission, RR increased significantly in males, obese patients, and in all age sub-groups ($p < 0.01$) except the young. At five days after admission, there were no significant differences between sex. During the whole five days of hospitalization, the overweight and obese sub-groups had higher RR as compared to the normal weight sub-group ($p < 0.01$). The young showed a significant increase ($p = 0.044$) in RR, and with no significant changes among the other sub-groups.

Heart rate (Figure 4d): During the first 48hrs, HR dropped among men, while increased among women ($p < 0.01$ and $p < 0.01$, respectively). From then on, the dynamics of HR behaved in opposite manners between sex, until day 5, in which both showed an increase, with males not reaching the baseline values and females showing a significant increase from baseline ($p < 0.01$). Young patients showed a mild

increase during the first 24hrs, remaining stable until day 5, during which the levels decreased back to baseline levels. Middle aged and elderly had a gradual decrease until day 4, and both increased to levels similar to those at baseline at day five. Patients over 80 years had peak increases at 24 and 48hrs after admission, followed by a sharp decrease to baseline levels in day 3, followed by an increase until the end of day 5. Though patients in the age groups started with the same baseline, after 24hrs the normal weight and obese started to show dynamic decrease until the 5th day, while the overweight had an overall increase.

Systolic Blood Pressure (Figure 4e): SBP showed similar trends among sex, with higher levels among males at day 4 after admission, returning to similar values by day 5. Changes in SBP over five days of hospitalization were significantly different between age groups ($p = 0.002$). The young showed a decrease in SBP during the first 24hrs, remaining relatively stable during the next three days, followed by an increase in SBP to a level higher than the baseline on day 5. The middle age and the elderly were relatively stable during the five days of monitoring. The over 80 years sub-group had higher SBP values during the whole period, increasing to peak levels by 48hrs, showing a relatively sharp decrease to baseline levels on day 4, and increasing back on day 5. Obese patients showed a decrease trend in SBP until day 4, increasing back to baseline levels on day 5. Normal weight and overweight patients showed a changing pattern with a decrease trend in SBP, both reaching nadir on day 4, and showing increase to baseline levels on day 5.

Diastolic Blood Pressure (Figure 4f): Both sexes showed a decrease in DBP values during the first 4 days, women to a higher extent than men ($p < 0.001$), and in the fifth day both showed increase with values among women returning to the baseline level. Patients over 80 years showed relatively lower DBP values during the 5 days period, reaching a nadir at day 4 ($p < 0.001$). The young and elderly showed a decrease trend in the first 3 days ($p < 0.01$), returning close to baseline levels by day 5. Though the middle age sub-group had the highest DBP levels, they also had a similar trend of decrease until day 4, returning close to baseline level on day 5. Normal weight patients had a sharp decrease during the first 24hrs ($p < 0.001$), maintaining this level until the 4th day, followed by a sharp increase during the 5th day to baseline levels. Both overweight and obese had a milder decrease during the first 4 days with overweight returning to baseline levels in the 5th day, and the obese returning to a lower level than the baseline ($p = 0.02$).

Cardiac Output (Figure 4g): Males had a sharp decrease in the first 24hrs ($p < 0.01$), kept stable in the next 48hrs, followed by a sharp decrease in the 4th day, and an increase in the 5th day to a level below baseline. Females showed dynamic changes reaching peak high levels on each of days one to three, followed by a drop shortly after every peak, followed by a constant increase until reaching the highest peak on day 5 ($p < 0.01$). Young patients showed stable CO values during the whole five-day period. Middle age and elderly showed a slight decrease during the first 24hrs, followed by a dynamic trend, with middle aged returning to the baseline levels while the elderly did not show significant changes from baseline ($p = 0.081$). Patients over 80 years had a dynamic pattern of changes with peaks at 24hrs and 48hrs from admission ($p < 0.01$ and $p = 0.02$, respectively), followed by lower peaks and increasing again at day 5 after admission. All BMI sub-groups had decreased levels of CO in the first 24hrs.

Cardiac Index (Figure 4h): Both sexes started with the same CI values at baseline. Shortly after, a sharp increase was evident amongst females reaching its peak at 48hrs after admission ($p < 0.001$), while amongst males a sharp decrease was seen after 24hrs ($p < 0.001$), maintained until day 4, in which a further decrease was evident, and a moderate increase appeared on day 5, to levels lower than baseline ($p < 0.001$). Amongst the young, dynamic changes were not statistically significant, with similar values to baseline measured on day 5. Both middle aged and elderly showed decreases within the first 24hrs ($p < 0.001$ in both). From that moment on, the middle aged showed moderate increase, becoming more pronounced on the 5th day, returning to baseline levels. However, amongst the elderly, further decrease was evident on day 4, increasing slightly on day 5 ($p < 0.001$). Unlike other age sub-groups, the over 80 years started with a sharp increase in CI during the first 24hrs, followed by a sharp decrease and immediately followed with a higher increase by 48hrs after admission ($p < 0.001$). This was followed by an unstable decrease over the next two days, and a sharp increase at day 5 ($p < 0.001$). Normal weight and overweight patients had dynamic non-significant changes in CI, with values similar to the baseline at the end of day 5. However, obese had a lower baseline level of CI, further decreasing during the first 24hrs, and reaching a nadir at day 5 ($p < 0.001$).

Systemic Vascular Resistance (Figure 4i): Females had a higher SVR value at baseline as compared with males, and during the 5-day period showed consistent decrease until the end of monitoring ($p < 0.001$). Males started with an increase during the first 24hrs ($p < 0.001$), and remained relatively stable until day 5. Over 80 years started at a higher level of SVR at baseline, and showed continuous decrease until day 5. Other age sub-groups started at the same baseline, with the middle age showing an increase in the first 24hrs ($p < 0.01$) followed by continuous decrease until day 5, returning to baseline level. The elderly remained stable until an increase on day 4, returning to baseline levels on day 5. The young showed dynamic decrease until a nadir on day 4, followed by an increase on day 5 back to baseline levels. Normal and obese patients had dynamic changes over the five-day period without significance. Overweight patients showed continuous decrease during the five-day period ($p < 0.01$).

Discussion

Frequently measured vital signs might help improve the understanding of the progression of COVID-19 in humans. So far, there were no reports detailing frequent monitoring of vitals in COVID-19 patients for prolonged periods of time, nor reports including advanced vitals such as CO, CI, and SVR, neither are there any reports that analyze how the disease influences vital sign trends. In Israel, many COVID-19 isolation units used (and are still using) a novel PPG-based platform for RPM (**Figure 1**). In the current multi-center study, we present the results of analyzing nine physiological parameters (temperature, SpO₂, RR, HR, SBP, DBP, CO, CI, and SVR) continuously monitored for five days in 130 COVID-19 patients within isolation units in five medical centers. This allowed an in-depth analysis and a more comprehensive understanding of the disease progression, focusing on sub-groups in danger of higher morbidity and mortality. It is established that advanced age, male sex, and overweight are worse prognostic factors in COVID-19 ³³⁻⁴⁰.

In this study, we show that this decline manifests upon admission with inferior cardiorespiratory parameters, and during the hospitalization period with increased average temperature in males, lower SpO₂, and increased RR in males, elderly patients and overweight patients.

We found that during the first 24hrs from admission the changes in the cardiovascular parameters appear in parallel to the changes in the respiratory parameters, an insight that was not reported previously. Moreover, the decrease found in DBP throughout most of the monitoring period might correlate with prior reports on diastolic dysfunction resulting from COVID-19 damage to the heart ^{21,22}, yet this hypothesis is still to be validated since we did not perform echocardiography. This could also be regarded as clinical deterioration, presented with concomitant decrease in CO and CI, and an increase in RR. The changes we found were more prominent amongst males, patients older than 80 years, and obese patients. This could also explain why patients with preexisting respiratory and cardiovascular diseases have an increased risk of severe morbidity and mortality ^{1,6,11-14,18,19,33,34,39,41-43}.

Previous studies employed periodic and infrequent biomarkers and echocardiography directed at cardiac injury. In this study, and for the first time, we used continuous and long-term monitoring of advanced cardiac parameters using a novel and non-invasive technology, previously showing its capabilities with similar measurements compared to invasive techniques ⁴⁴. We found several interesting components to the cardiovascular changes, such as a decrease in CI among the risk populations (e.g. male, elderly and obese patients) after five days of monitoring, dropping to lower than the normal range in males, in addition to an increase in SVR among these populations. Previously published data showed direct damage to the heart and its function, as well as thrombogenesis which might influence the SVR. However, we do not have sufficient data on these parameters, in COVID-19 patients or on the general population, and this should be studied further.

Another behavior of note is that the trends seen in HR, SBP, CO, and CI seem to be repetitive (**Figure 3 and 4**). This might be part of a circadian rhythm, yet again – we do not have enough data to substantiate this observation, and it should be further studied.

Significant changes between the studied groups were already apparent during the 2-hour baseline period, emphasizing that physiological effects of COVID-19 are different among the various groups beyond the expected naturally-occurring differences.

Although statistically significant changes were found in some vitals among the groups, they were slight and are currently not considered to be of clinical significance. However, we think that as advanced monitoring tools will keep developing and being introduced into clinical practice, amplified by advanced AI and machine learning analysis tools, we may find that even these slight changes could have significance and warrant clinical attention, especially when developing early warning score systems in the context of complex patients.

Operationally, the continuously collected data was transferred automatically and in real-time every 15 minutes to the medical staff. This reduced the direct contact between medical staff and patients without compromising the medical care provided, an important feature highly required during a pandemic.

When looking at the ambulatory and out-of-hospital environments, the early identification of symptomatic and pre-symptomatic infected individuals would be especially valuable in breaking chains of infections, principally due to increased transmission during this period ⁴⁴⁻⁴⁷. A small wearable, wireless RPM device that frequently collects and transmits the data automatically and in real-time could help in achieving that. Moreover, by using this technology with COVID-19 patients we now have an opportunity to define a novel COVID-19 score for the accurate early detection of deterioration. Due to sex-, age-, and BMI-related differences in disease progression ³³⁻⁴⁰, it might be prudent to define a separate score for individuals based on their basic characteristics. This tailored precision medicine approach should be further studied.

A limitation of this study is that we did not have the clinical data regarding the course of hospitalization and final outcomes of these patients. All were admitted to isolation units in moderate to severe condition, and some were later transferred to COVID-19 dedicated ICUs. We have no information regarding outcomes, administration of supplemental oxygen, vasopressors, and specific therapeutics against COVID-19. However, they all received advanced medical care, and the number of data points of multiple physiological parameters collected was large and frequent, still allowing to have insights of clinical significance. On-going studies are now conducted in order to allow the parallel analysis of collected vitals and clinical data.

In conclusion, in this study we have shown for the first time the trajectories of cardiorespiratory parameters during a long period of frequent monitoring using an RPM system. Using advanced bioinformatic tools we demonstrate that populations at risk display worse respiratory parameters, as well as worse advanced cardiovascular parameters, emphasizing the cardiorespiratory effects of COVID-19 over time, with differential physiological responses noted between sex, BMI and age groups. This may serve to improve early detection of clinical deterioration of COVID-19 patients, especially important in times of overwhelmed health care systems, helping to reduce direct contact between health care providers and COVID-19 patients without compromising medical care.

Methods

Study Design and Overview

This retrospective non-interventional study was conducted between March 3rd, 2020 and May 22nd, 2020. 571 COVID-19 patients were hospitalized immediately upon admission into five COVID-19 dedicated isolation units in Israel. All were automatically and continuously monitored using non-invasive, wearable, and wireless photoplethysmography (PPG)-based chest-monitors. The monitors were attached and activated upon admission, with measurements automatically taken every 15 minutes and transmitted in real-time to a cloud-based web application used by the medical staff (**Figure 1**). Data collection and analysis was approved by the relevant institutional review boards (approvals 0077-20-WOMC; 0048-20-POR; 0506-20-RMB; 0193-20-KMC; 0421-20-SOR), and patient consent was waived.

Designated gateways (BB-SGWB Smart Gateway Box/BB-90000300100, Biobeat Technologies Ltd.) were installed in the isolation units to ensure continuous monitoring and data transmission of all measurements (**Figure 1**). Physiological parameters included in the analysis were HR, SpO₂, RR, cuff-less non-invasive BP (including SBP and DBP), CO, CI, SVR, and body temperature.

PPG-based Device

The chest-monitor device used in this study (**Figure 1**) utilizes a unique reflective PPG technology, in which specific wavelengths of light are transmitted onto skin tissue, reflected from the tissue and detected by a photodiode detector positioned near the light source transmitter. The sensor tracks vital signs derived from changes in the pulse contour, following a simple offset baseline trimonthly calibration process using an approved non-invasive, cuff-based device, and is based on Pulse Wave Transit Time (PWTT) technology combined with Pulse Wave Analysis (PWA) ^{25,48,49}.

Patients were monitored throughout hospitalization time, and patches were replaced if hospitalization lasted longer than the 6-day battery life of the patch. Same patches were not used to monitor different patients.

Statistical analysis

Global outliers were picked using PCA and histogram examination. On a per-patient level, outlier observations with difference from the mean that's greater than $Q3 + 3 \times IQR$, were discarded.

All statistical analyses were made using R version 3.6.3⁵⁰. Differences between the studied groups were determined using independent t-test when the data satisfied test requirements. Equal variances were assumed if Barlett and Levene tests came out significant. Wilcox test was performed for metrics with non-normal distribution. For key physiological variables recorded during the first 2hrs of admission, normality was assessed using the Shapiro test QQ-plots, allowing the removal of extreme outliers. Then, differences between groups were determined using repeated measures ANOVA. Where a significant main effect was found, a Tukey's *post hoc* test was performed. The data was fitted to a linear mixed model with nlme 3.1, with sex, age range and BMI as coefficients, then tested using ANOVA. Pairwise Wilcox was used for post-hoc testing when the sample-sizes were sufficiently large ($n > 50$). Trend estimation figures with less than 1,000 observations were done using loess, while larger trend data was done using gam. All other results are presented as means $\pm$ SD. Statistical analyses were considered significant if $p < 0.05$.

Declarations

Ethics Declarations

Retrospective data collection and analysis was approved by a multi-center institutional review board (approval numbers 0077-20-WOMC; 0048-20-POR; 0506-20-RMB; 0193-20-KMC; 0421-20-SOR), and patient consent was waived.

Funding Source

None.

References

1. Zhou, F. *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet* (2020).
2. Libby, P. & Lüscher, T. COVID-19 is, in the end, an endothelial disease. *Eur. Heart J.* **41**, 3038–3044 (2020).
3. Tikellis, C. & Thomas, M. C. Angiotensin-converting enzyme 2 (ACE2) is a key modulator of the renin angiotensin system in health and disease. *Int. J. Pept.* **2012**, (2012).
4. Zhang, H., Penninger, J. M., Li, Y., Zhong, N. & Slutsky, A. S. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intensive Care Med.* **46**, 586–590 (2020).
5. Bhatraju, P. K. *et al.* Covid-19 in critically ill patients in the Seattle region—case series. *N. Engl. J. Med.* **382**, 2012–2022 (2020).
6. Wang, D. *et al.* Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *Jama* **323**, 1061–1069 (2020).
7. Li, Y.-C., Bai, W.-Z. & Hashikawa, T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J. Med. Virol.* **92**, 552–555 (2020).
8. Mao, L. *et al.* Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. (2020).
9. Clerkin, K. J. *et al.* COVID-19 and cardiovascular disease. *Circulation* **141**, 1648–1655 (2020).
10. Fosbøl, E. L. *et al.* Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with COVID-19 diagnosis and mortality. *Jama* **324**, 168–177 (2020).
11. Guo, T. *et al.* Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol.* (2020).
12. Lindner, D. *et al.* Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases. *JAMA Cardiol.* (2020).
13. Richardson, S. *et al.* Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *Jama* (2020).
14. Zheng, Y.-Y., Ma, Y.-T., Zhang, J.-Y. & Xie, X. COVID-19 and the cardiovascular system. *Nat. Rev. Cardiol.* **17**, 259–260 (2020).
15. Babapoor-Farrokhran, S. *et al.* Myocardial injury and COVID-19: Possible mechanisms. *Life Sci.* 117723 (2020).
16. Bonow, R. O., O’Gara, P. T. & Yancy, C. W. Cardiology and COVID-19. *JAMA* **324**, 1131–1132 (2020).
17. Nishiga, M., Wang, D. W., Han, Y., Lewis, D. B. & Wu, J. C. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. *Nat. Rev. Cardiol.* 1–16 (2020).
18. Puntmann, V. O. *et al.* Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol.* (2020).
19. Giustino, G. *et al.* Coronavirus and Cardiovascular Disease, Myocardial Injury, and Arrhythmia. *J. Am. Coll. Cardiol.* **76**, 2011–2023 (2020).
20. Lavie, C. J., Sanchis-Gomar, F. & Lippi, G. *Cardiac Injury in COVID-19—Echoing Prognostication*. (American College of Cardiology Foundation Washington DC, 2020).
21. Kim, J. *et al.* Prognostic utility of right ventricular remodeling over conventional risk stratification in patients with COVID-19. *J. Am. Coll. Cardiol.* **76**, 1965–1977 (2020).
22. Pellikka, P. A. & Naqvi, T. Z. *The Right Ventricle: A Target in COVID-19 Cardiac Insult*. (American College of Cardiology Foundation Washington DC, 2020).

23. Giustino, G. *et al.* Characterization of myocardial injury in patients with COVID-19. *J. Am. Coll. Cardiol.* **76**, 2043–2055 (2020).
24. Berlin, D. A., Gulick, R. M. & Martinez, F. J. Severe Covid-19. *N. Engl. J. Med.* NEJMcp2009575 (2020) doi:10.1056/NEJMcp2009575.
25. Halberthal, M., Nachman, D., Eisenkraft, A. & Jaffe, E. Hospital and home remote patient monitoring during the COVID-19 outbreak: A novel concept implemented. *Am. J. Disaster Med.* **15**, 149–151 (2020).
26. Posthuma, L. M. *et al.* Remote wireless vital signs monitoring on the ward for early detection of deteriorating patients: A case series. *Int. J. Nurs. Stud.* **104**, 103515 (2020).
27. Keesara, S., Jonas, A. & Schulman, K. Covid-19 and health care's digital revolution. *N. Engl. J. Med.* **382**, e82 (2020).
28. Watkinson, P. J. *et al.* A randomised controlled trial of the effect of continuous electronic physiological monitoring on the adverse event rate in high risk medical and surgical patients. *Anaesthesia* **61**, 1031–1039 (2006).
29. Churpek, M. M., Adhikari, R. & Edelson, D. P. The value of vital sign trends for detecting clinical deterioration on the wards. *Resuscitation* **102**, 1–5 (2016).
30. Taenzer, A. H., Perreard, I. M., MacKenzie, T. & McGrath, S. P. Characteristics of desaturation and respiratory rate in postoperative patients breathing room air versus supplemental oxygen: Are they different? *Anesth. Analg.* **126**, 826–832 (2018).
31. Lin, B.-S., Wong, A. M. & Tseng, K. C. Community-based ECG monitoring system for patients with cardiovascular diseases. *J. Med. Syst.* **40**, 80 (2016).
32. Tung, C. E., Su, D., Turakhia, M. P. & Lansberg, M. G. Diagnostic yield of extended cardiac patch monitoring in patients with stroke or TIA. *Front. Neurol.* **5**, 266 (2015).
33. Baronio, M. *et al.* Italian SARS-CoV-2 patients in intensive care: towards an identikit for subjects at risk? *Eur. Rev. Med. Pharmacol. Sci.* **24**, 9698–9704 (2020).
34. Chinnadurai, R. *et al.* Older age and frailty are the chief predictors of mortality in COVID-19 patients admitted to an acute medical unit in a secondary care setting-a cohort study. *BMC Geriatr.* **20**, 1–11 (2020).
35. Hussain, A., Mahawar, K., Xia, Z., Yang, W. & Shamsi, E.-H. Obesity and mortality of COVID-19. Meta-analysis. *Obes. Res. Clin. Pract.* (2020).
36. Popkin, B. M. *et al.* Individuals with obesity and COVID-19: A global perspective on the epidemiology and biological relationships. *Obes. Rev.* (2020).
37. Pradhan, A. & Olsson, P.-E. Sex differences in severity and mortality from COVID-19: are males more vulnerable? *Biol. Sex Differ.* **11**, 1–11 (2020).
38. Smati, S. *et al.* Relationship between obesity and severe COVID-19 outcomes in patients with type 2 diabetes: results from the CORONADO study. *Diabetes Obes. Metab.*
39. Spagnolo, P. A., Manson, J. E. & Joffe, H. *Sex and gender differences in health: What the COVID-19 pandemic can teach us.* (American College of Physicians, 2020).
40. Soeroto, A. Y. *et al.* Effect of increased BMI and obesity on the outcome of COVID-19 adult patients: A systematic review and meta-analysis. *Diabetes Metab. Syndr. Clin. Res. Rev.* (2020).
41. Huang, C. *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet* **395**, 497–506 (2020).
42. Topol, E. J. COVID-19 can affect the heart. *Science* (2020).
43. Li, B. *et al.* Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin. Res. Cardiol.* **109**, 531–538 (2020).
44. Chau, N. V. V. *et al.* The natural history and transmission potential of asymptomatic SARS-CoV-2 infection. *medRxiv* (2020).
45. Jing, Q.-L. *et al.* Household secondary attack rate of COVID-19 and associated determinants in Guangzhou, China: a retrospective cohort study. *Lancet Infect. Dis.* **20**, 1141–1150 (2020).
46. Quer, G. *et al.* Wearable sensor data and self-reported symptoms for COVID-19 detection. *Nat. Med.* 1–5 (2020).
47. Ferretti, L. *et al.* Quantifying SARS-CoV-2 transmission suggests epidemic control with digital contact tracing. *Science* **368**, (2020).
48. Nachman, D. *et al.* Wireless, Non-Invasive, Wearable Device for Continuous Remote Monitoring of Hemodynamic Parameters in a Swine Model of Controlled Hemorrhagic Shock. *Sci. Rep. In Press*, (2020).
49. Nachman, D. *et al.* Comparing blood pressure measurements between a photoplethysmography-based and a standard cuff-based manometry device. *Sci. Rep.* **10**, 1–9 (2020).
50. R Core Team. *R: A Language and Environment for Statistical Computing.* (R Foundation for Statistical Computing, 2015).

Table

Table 1. Patient characteristics and average values by sub-groups for the first 2 hours of monitoring

Variable	Sex		Age				<i>p</i>	BMI			<i>p</i>
	Male	Female	Young (18-40 years)	Middle age (40-60 years)	Elderly (60-80 years)	> 80 years		Normal <24.9 kg•min ⁻²	Overweight 25.0-29.9 kg•min ⁻²	Obese >30.0 kg•min ⁻²	
<i>n</i>	313	179	131	128	171	62		198	171	123	
Sex M:F			84:47	89:39	113:58	27:35		111:87	122:49	80:43	
Monitoring period (hours)	95.4 ± 67.6	83.5 ± 62.6	64.9 ± 43.7	87.8 ± 49.8	101.5 ± 69.3	120.7 ± 97.9		86.6 ± 69.1	98.1 ± 64.1	88.0 ± 63.2	
Age (years)	56 ± 17	60 ± 22	31 ± 6 _{b,c,d}	53 ± 5 _{a,c,d}	69 ± 6 _{a,b,d}	87 ± 5 _{a,b,c}	*	53 ± 20 _{&^}	61 ± 18 [#]	59 ± 17 [#]	*
Weight (kg)	83.1 ± 14.5	71.0 ± 15.5	75.7 ± 17.6 ^b	83.0 ± 14.6 _{a,c,d}	78.8 ± 16.5 ^b	75.1 ± 11.1 ^b	*	67.2 ± 10.3 _{&^}	80.1 ± 9.0 [#]	95.3 ± 16.3 [#]	*
BMI (kg•m ⁻²)	27.26 ± 4.49	26.83 ± 5.92 ^{\$}	25.3 ± 5.33 _{b,c,d}	28.25 ± 4.49 ^a	27.2 ± 5.36 ^a	27.63 ± 3.81 _a	*	22.74 ± 2.18 _{&^}	27.41 ± 1.36 [#]	33.67 ± 4.54 [#]	*
Body temp. (C)	37.3 ± 0.7	37.2 ± 0.6 ^{\$}	37.2 ± 0.6 ^d	37.3 ± 0.7	37.4 ± 0.7 ^d	37.2 ± 0.7 _{a,c}	*	37.3 ± 0.6	37.3 ± 0.7	37.3 ± 0.7	
SpO ₂ (%)	95.4 ± 3.3	95.9 ± 2.9 ^{\$}	96.7 ± 2.4 _{b,c,d}	95.0 ± 3.3 _{a,c}	95.1 ± 3.2 _{a,b,d}	95.7 ± 3.3 _{a,c}	*	96.0 ± 2.9 _{&^}	95.5 ± 3.0 ^{#,^}	95.0 ± 3.6 _{#,&}	*
RR (br•min ⁻¹)	17.5 ± 4.2	17.1 ± 3.7	15.7 ± 3.7 _{b,c,d}	18.1 ± 4.1 _{a,d}	18.0 ± 4.0 ^a	17.1 ± 3.7 _{a,b}	*	17.2 ± 4.0 [^]	17.0 ± 4.0 [^]	18.1 ± 4.2 _{#,&}	*
HR (beats•min ⁻¹)	83 ± 14	81 ± 14 ^{\$}	83 ± 15 ^d	84 ± 14 ^d	82 ± 13 ^d	79 ± 14 _{a,b,c}	*	83 ± 13 [^]	83 ± 14	81 ± 5 [#]	
SBP (mmHg)	129 ± 17	128 ± 20	126 ± 15 _{c,d}	128 ± 18 ^d	130 ± 20	132 ± 23 _{a,b}	*	129 ± 18	128 ± 17	129 ± 20	
DBP (mmHg)	77 ± 13	75 ± 11 ^{\$}	77 ± 11.7 _{c,d}	78 ± 12 ^d	75 ± 12 _{c,d}	72 ± 13 _{a,b,c}	*	76 ± 12	76 ± 13	76 ± 12	
CO (l•min ⁻¹)	5.9 ± 1.4	5.7 ± 1.4 ^{\$}	6.0 ± 1.6 ^d	5.9 ± 1.3 ^d	5.8 ± 1.3 ^d	5.4 ± 1.2 _{a,b,c}	*	5.9 ± 1.5 [^]	5.9 ± 1.4 [^]	5.6 ± 1.2 _{#,&}	*
CI (L•min ⁻¹ •m ⁻²)	3.1 ± 0.9	3.2 ± 0.9	3.3 ± 1.0 _{b,c,d}	3.1 ± 0.8 ^a	3.2 ± 0.8 _{a,d}	2.9 ± 0.8 _{a,c}	*	3.4 ± 0.9 _{&^}	3.1 ± 0.8 _{#,^}	2.8 ± 0.8 _{#,&}	*
SVR (dynes•sec ⁻¹ •cm ⁻⁵)	1311 ± 277	1341 ± 295	1295 ± 291 ^d	1319 ± 253 ^d	1313 ± 277 ^d	1401 ± 336 _{a,b,c}	*	1309 ± 291	1317 ± 284	1350 ± 269	
Values as mean±SD representing each patient's entire monitoring period (mean ± SD hrs of monitoring; range: 24-225 hours). BMI: body mass index; temp.: temperature; SpO ₂ : oxyhemoglobin saturation; RR: respiratory rate; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; CO: cardiac output; CI: cardiac index; SVR: systemic vascular resistance. * Significant interaction (within group comparison), <i>p</i> < 0.05; ^{\$} Female significantly different than male, <i>p</i> < 0.05; _{a,b,c,d} significantly different than young, middle age, elderly, >80 years within age categories, <i>p</i> < 0.05; ^{#,&^} significantly different than normal, overweight, obese withing BMI categories, <i>p</i> < 0.05											

Figures

Figure 1

The remote patient monitoring (RPM) system deployed in isolation units. The chest-patch sensor was attached to all moderate to severe COVID-19 patients included in the study. This RPM system provides automatic measurement of 15 vital signs every 5 to 15 minutes. Data is transmitted through Bluetooth low energy (BLE) from the sensors (A) to gateways (B) installed in the isolation units and from there through Wi-Fi or a SIM card to a cloud-based medical management application available to health care providers on any web platform (C), allowing to monitor all admitted patients at once. The monitor shows the vital signs in real-time, provides alerts, and has an integrated early warning score system.

Figure 2

Number of subjects per group throughout the entire monitoring period. A) division by sex; B) division by age-groups (young: 18-40 years; middle age: 40-60 years; elderly: 60-80 years; >80 years); C) division by body mass index (BMI; normal weight: <24.9 kg•min⁻²; overweight: 25-29.9 kg•min⁻²; obese: >30 kg•min⁻¹). The breakdown of patients' numbers by day was 492 at 24hrs, 408 at 48hrs, 294 at 72hrs, 204 at 86hrs, 130 at 120hrs, 92 at 144hrs, 66 at 168hrs, 49 at 192hrs, 43 at 216hrs, 33 at 240hrs, and 21 at 264hrs.

Figure 3

Average recorded measurements among 130 patients continuously monitored for 5 days from admission, without separation to sub-groups. Temp, temperature; SpO2, blood oxygen saturation; RR, respiratory rate; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; CO, cardiac output; CI, cardiac index; SVR, systemic vascular resistance. The blue line represents mean value of each vital and the 95% confidence interval appears in gray.

Figure 4

Measured vital signs by Sex, BMI and Age group, over the course of the first 5 days of tracking. Definitions of BMI and Age groups are provided in Figure 2. Temp, temperature; SpO2, blood oxygen saturation; RR, respiratory rate; HR, heart rate, SBP, systolic blood pressure; DBP, diastolic blood pressure; CO, cardiac output; CI, cardiac index; SVR, systemic vascular resistance. Each line represents mean values of the vitals and 95% confidence interval appears in gray.