Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company’s public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Decreased serial scores of severe organ failure assessments are associated with survival in mechanically ventilated patients; the prospective Maastricht Intensive Care COVID cohort

Julia L.M. Bels a,f, Sander M.J. van Kuijk b, Chahinda Ghossein-Doha a,c,l, Fabian H. Tijssen d, Rob J.J. van Gassel a,e,f, Jeanette Tas a,g, MaastrICcht Collaborators a, Ronny M. Schnabel a, Marcel J.H. Aries a,g, Marcel C.G. van de Poll a,e,f, Dennis C.J.J. Bergmans a, Steven J.R. Meex h,i, Walther N.K.A. van Mook a,i, Iwan C.C. van der Horst a,j, Bas C.T. van Bussel a,k,*

a Dep. of Intensive Care, Maastricht University Medical Centre+; b Dep. of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre+; c Dep. of Cardiology, Maastricht University Medical Centre+; d Dep. of Surgery, Maastricht University Medical Centre+; e Dep. of Anaesthesiology and Pain Medicine, Maastricht University Medical Centre+; f Dep. of Nephrology, Maastricht University Medical Centre+; g School of Nutrition and Translational Research in Metabolism (NUTRIM), Maastricht University; h School of Mental Health and Neuroscience (MHeNS), Maastricht University Medical Centre+; i Department of Clinical Chemistry, Central Diagnostic Laboratory, Maastricht University Medical Centre+; j School of Health Professions Education, Maastricht University Medical Centre+; k Cardiovascular Research Institute Maastricht (CARIM), Maastricht University; l Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre+.

© 2020 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Keywords: Cohort study; Repeated data; COVID-19; Multi-organ failure; SOFA score; SARS-CoV-2

Background: The majority of patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are admitted to the Intensive Care Unit (ICU) for mechanical ventilation. The role of multi-organ failure during ICU admission as driver for outcome remains to be investigated yet.

Design and setting: Prospective cohort of mechanically ventilated critically ill with SARS-CoV-2 infection.

Participants and methods: 94 participants of the MaastrICcht cohort (21% women) had a median length of stay of 16 days (maximum of 77). After division into survivors (n = 59) and non-survivors (n = 35), we analysed 1555 serial SOFA scores using linear mixed-effects models.

Results: Survivors improved one SOFA score point more per 5 days (95% CI: 4.94–8) than non-survivors. Adjustment for age, sex, and chronic lung, renal and liver disease, body-mass index, diabetes mellitus, cardiovascular risk factors, and Acute Physiology and Chronic Health Evaluation II score did not change this result. This association was stronger for women than men (P-interaction = 0.043).

Conclusions: The decrease in SOFA score associated with survival suggests multi-organ failure involvement during mechanical ventilation in patients with SARS-CoV-2. Surviving women appeared to improve faster than surviving men. Serial SOFA scores may unravel an unfavourable trajectory and guide decisions in mechanically ventilated patients with SARS-CoV-2.

© 2020 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

List of abbreviations

- **ABSTRACT**

| Abbreviation | Description |
|--------------|-------------|
| SOFA | Sequential Organ Failure Assessment |
| GCS | Glasgow Coma Scale |
| FiO2 | Fraction of inspired oxygen |
| BMI | Body Mass Index |
| CI | Confidence interval |
| CORADS | COVID-19 Reporting and Data System |
| APACHE II | Acute Physiology and Chronic Health Evaluation II |
| GCS | Glasgow Coma Scale |

Keywords: Cohort study; Repeated data; COVID-19; Multi-organ failure; SOFA score; SARS-CoV-2

Background: The majority of patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are admitted to the Intensive Care Unit (ICU) for mechanical ventilation. The role of multi-organ failure during ICU admission as driver for outcome remains to be investigated yet.

Design and setting: Prospective cohort of mechanically ventilated critically ill with SARS-CoV-2 infection.

Participants and methods: 94 participants of the MaastrICcht cohort (21% women) had a median length of stay of 16 days (maximum of 77). After division into survivors (n = 59) and non-survivors (n = 35), we analysed 1555 serial SOFA scores using linear mixed-effects models.

Results: Survivors improved one SOFA score point more per 5 days (95% CI: 4.94–8) than non-survivors. Adjustment for age, sex, and chronic lung, renal and liver disease, body-mass index, diabetes mellitus, cardiovascular risk factors, and Acute Physiology and Chronic Health Evaluation II score did not change this result. This association was stronger for women than men (P-interaction = 0.043).

Conclusions: The decrease in SOFA score associated with survival suggests multi-organ failure involvement during mechanical ventilation in patients with SARS-CoV-2. Surviving women appeared to improve faster than surviving men. Serial SOFA scores may unravel an unfavourable trajectory and guide decisions in mechanically ventilated patients with SARS-CoV-2.

© 2020 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (also called COVID-19) is highly heterogeneous in its presentation [1-3]. Approximately 40% of patients are asymptomatic and 40% have mild illness, while around 20% require hospitalization, of whom 5–10% become critically ill requiring mechanical ventilation [4]. The current COVID-19 pandemic maximally stresses Intensive Care resources in many countries, as recently seen in the Netherlands [5,6]. The SARS-CoV-2 disease course in mechanically ventilated patients is however largely unknown.

At first, SARS-CoV-2 infection appeared a severe respiratory infection only [2]. However, more recent data suggest that thrombosis, affecting the cardiovascular system, plays a significant additional role in complicating the disease course [7,8]. Data on other organ system failures complicating the course of the disease are scarce [9-25]. Most likely, this multi-organ involvement occurs independent of comorbidities, as SARS-CoV-2 infection is an intercurrent disease, affecting the general population [6].

Progressive multi-organ disease increases mortality, although it may be heterogeneous over time and vary between and within individual patients. For example, data suggest that women are less severely affected by SARS-CoV-2 infection than men [3,14]. The course of multi-organ disease could, therefore, also potentially differ between men and women. Furthermore, changes in the number and severity of organ systems involved over time may also include valuable prognostic information that may guide clinical decisions for mechanically ventilated patients.

The Sequential Organ Failure Assessment (SOFA) score, widely established to determine multi-organ failure in Intensive Care Unit (ICU) patients, is designed to evaluate changes in organ failure over time [26-28]. The SOFA score includes components reflective of the respiratory, coagulation, liver, cardiovascular, renal, and central nervous systems. Whether trends in SOFA score during ICU admission are associated with outcome remains to be established for SARS-CoV-2 infection [29].

2. Methods

The manuscript was written following the STrengthening the Reporting of OBServational studies in Epidemiology (STROBE) guideline [30].

2.1. Participants

The Maastricht Intensive Care COVID (MaastrICCht) cohort study design has been described more extensively elsewhere [31]. Briefly, this prospective cohort study was conducted in patients admitted to the Intensive Care of the Maastricht University Medical Centre+ (Maastricht UMC+), a tertiary care university teaching hospital in the southern part of the Netherlands. Usually, the Maastricht UMC+ ICU has 27 beds, divided over three subunits to which all types of critically ill patients are admitted. During the COVID-19 pandemic, our ICU was rapidly step-wise upgraded to a maximum of 64 beds, consisting of six subunits with 52 beds for COVID-19 patients and two subunits with 12 beds for non-COVID Intensive Care patients. The study was designed to foster other datasets and registries according to the FAIR data principle in collaboration [31]. The local institutional review board (Medisch Ethische Toetsingscomissie (METC) 2020-1565/ 300523) of the Maastricht UMC+ approved the study, which was performed based on the regulations of Helsinki. During the pandemic, the board of directors of Maastricht UMC+ adopted a policy to inform patients and ask their consent to use the collected data and stored left-over serum samples for COVID-19 research purposes. The study is registered in the Netherlands Trial Register (registration number NL8613).

This study included all participants with respiratory insufficiency requiring mechanical ventilation and at least one PCR positive for SARS-CoV-2 and/or a chest CT scan strongly suggestive for SARS-CoV-2 infection, based on a CORADS-score of 4–5 scored by a radiologist [32]. Participants were followed until primary outcome was reached (i.e. either death in the ICU or discharge from the ICU). After training by qualified research staff and with daily supervision by a senior investigator, medical research interns and PhD candidates not involved in patient care included participants and collected clinical, physiological, and laboratory variables using a predefined study protocol (extensively described elsewhere) [31]. For the present study, participants were included from March the 25th, the inception of the cohort, until June the 23rd 2020.

2.2. Multi-organ failure variables

Within the MaastrICCht cohort every component of the SOFA score was collected daily in mechanically ventilated patients with a SARS-CoV-2 infection [31]. The SOFA score includes components reflecting the status of coagulation, the liver and the respiratory, cardiovascular, central nervous, and renal organ systems. Each organ system component is scored as one of five categories, ranging from 0 (normal organ function) to 4 (worst organ function). The SOFA score is the sum of the six organ system component scores and thus ranges from 0 to 24. The SOFA score was developed to evaluate multi-organ function daily, which is a major advantage to study the development of multi-organ failure over time [26]. Evidence for SARS-CoV-2 infection, and definition of SOFA score and its components are shown in Table 1.

2.3. Outcome variables

The study population was divided into two subgroups, participants who had died during their ICU stay and participants who were discharged from the ICU alive.

2.4. Confounders

Comorbidities were proposed as confounder as these can be associated with organ function at baseline and determine patient outcome [33]. For the present study, in addition to age and sex, chronic lung, liver and renal disease, and COVID-19 related comorbidities, such as obesity (body mass index, BMI kg/m²), diabetes mellitus, and presence of cardiovascular risk factors, present on admission, were considered as potential confounders. Furthermore, we considered the admission Acute Physiology and Chronic Health Evaluation II (APACHE II) score as a potential confounder. The APACHE II score is a physiologically based classification system for measuring severity of illness in groups of critically ill patients [34]. APACHE II and SOFA score differ, although both score severity of critical illness. The APACHE II score was primarily developed to rank disease severity between patients over the first 24 h of
admission, whereas the SOFA score was developed to monitor disease severity within a patient over time [26].

2.5. Statistical analyses

The sample size was determined pragmatically; all participants eligible for the study that had been enrolled in the cohort until June the 23rd 2020 were included. The data were analysed with R version 3.6.1. The sample characteristics were described using mean and standard deviation (SD), median and interquartile range (IQR), or percentage, as appropriate.

First, the cohort was categorised into ICU-survivors and ICU-non-survivors. All participants reached a primary outcome. We computed estimates of group differences in the trajectory of average SOFA scores over time between those discharged alive, and those who had died. Next, we used linear mixed-effects regression with a random intercept and random slope with time to compute differences in average SOFA scores and differences in the slope over time between both groups. Specifically, we used unstructured variance-covariance matrix and an autoregressive correlation structure of the first order for longitudinal measures. To assess non-linear change over time, we added polynomial terms of time. Using the Akaike Information Criterion, the best model for change over time was selected. To assess non-linear change over time, we added polynomial terms of time. Using the Akaike Information Criterion, the best model for change over time was selected. To assess non-linear change over time, we added polynomial terms of time. Using the Akaike Information Criterion, the best model for change over time was selected. To assess non-linear change over time, we added polynomial terms of time. Using the Akaike Information Criterion, the best model for change over time was selected.

We computed the crude group differences (Model 1). Next, the model was adjusted for age and sex (Model 2), and additionally for COVID-19 related comorbidities such as obesity (BMI), diabetes...
mellitus, and the presence of cardiovascular risk factors and chronic lung disease, chronic liver disease, and chronic renal disease at baseline (Model 3). Subsequently, model 3 was adjusted for the APACHE II score (Model 4), to further disentangle patient disease severity (APACHE II) from within patient disease severity over time (SOFA score) in the association between disease severity and outcome. We also tested for effect-modification of the association between SOFA score over time and outcome by sex by adding a three-way interaction term to Model 2.

As twelve participants were transferred from ICU because of logistical reasons, we conducted a sensitivity analyses and repeated the main analyses without those 12. We checked the percentage of missing values for all potential confounding variables as determined in the previously published protocol [31]. Data would be imputed if the proportion of incomplete patients is over 5%, excluding the longitudinal measures as they were analysed using generalised linear mixed-effects regression. In case of over 5% of incomplete records, multiple imputation would be performed.

### 3. Results

The MaastrICCht cohort includes a total of 94 participants at the time of data extraction. The mean age was 64.3 ± 11.9 years, 21% were women. In total, 1555 serial SOFA scores had been recorded, with a mean of 7.7 ± 2.3 on admission. The mean APACHE II score on admission was 15.8 ± 5.7. Correlation coefficient between SOFA score and APACHE II score on admission was 0.54. All participants reached primary outcome, one of which did not contribute any SOFA score. Of the 93 participants included in the analyses, 35 (38%) had died and 58 were discharged alive (supplemental Fig. S1). The median duration of stay in the ICU was 16 days (1st and 3rd quartile: 8 and 24 days), with a maximum of 77 days. Table 2 shows the characteristics of the included participants stratified by primary outcome. Of all confounding variables, only BMI was missing in 1 (1%) participant. Hence, no data imputation was performed.

| ICU-survivors (n = 58) | ICU-non-survivors (n = 35) | p-value for difference |
|------------------------|--------------------------|-----------------------|
| Age, year              | 61.4 (12.2)              | 68.9 (9.8)            | 0.003      |
| Sex, men               | 43 (74%)                 | 30 (86%)              | 0.188      |
| Time of ICU stay, days  | 19 (9; 33)               | 14 (3; 17)            | 0.004b     |
| Height, cm             | 175.5 (9.2)              | 175.0 (8.6)           | 0.806      |
| Weight, kg             | 85.9 (13.8)              | 83.1 (12.6)           | 0.339      |
| Body mass index, kg/m² | 27.3 (4.2)               | 27.2 (3.9)            | 0.404      |
| Admission location:    |                          |                       | 0.925      |
| Emergency room         | 14 (24%)                 | 8 (23%)               |            |
| Ward                   | 28 (48%)                 | 16 (46%)              |            |
| Transfer from other hospital | 16 (28%) | 11 (31%) |            |
| Liver disease          | 1 (2%)                   | 0 (0%)                | 1.000b     |
| Chronic lung disease   | 4 (7%)                   | 4 (11%)               | 0.469b     |
| Chronic renal disease  | 1 (2%)                   | 1 (3%)                | 1.000b     |
| Diabetes mellitus type 2 | 7 (12%)       | 7 (20%)               | 0.300      |
| Presence of any cardiovascucl risk factor (i.e. hypertension, dyslipidaemia, smoking, obesity) | 24 (41%) | 21 (60%) | 0.082      |

Data are presented as mean (standard deviation) or count (percentage), unless indicated otherwise. Differences were tested using the independent-samples t-test or Pearson’s chi-square test, unless indicated otherwise. ICU, Intensive Care Unit.

Fig. 1. SOFA scores over time in ICU-survivors and ICU-non-survivors. A lower SOFA score indicates less organ dysfunction.
the ICU (p-value for difference: 0.068). Fig. 1 shows the individual trajectories of observed SOFA scores for ICU-survivors and ICU-non-survivors. Fig. 2 shows the observed SOFA scores for ICU-survivors and ICU-non-survivors throughout follow-up, with lines superimposed showing the best-fitting overall trajectories over time, unadjusted for confounders. On average, ICU-survivors had a lower overall SOFA score during their ICU stay (regression coefficient: −1.49, 95% CI: −2.48; −0.50), and improved more over time as indicated by the steeper slope and significant interaction between group and time (−0.19 per day, 95% CI: −0.25; −0.12) as compared to ICU-non-survivors (decreasing SOFA score indicates improving organ function) (Table 3, Model 1; and Fig. 1). Fig. 3 shows development of categories of SOFA scores over weeks for ICU-survivors and ICU-non-survivors. A lower SOFA score indicates less organ dysfunction.

Table 3

Results of linear mixed-effects models: difference in SOFA score development between ICU-survivors and ICU-non-survivors.

| Model | Regression coefficient (95% CI) | p-value |
|-------|---------------------------------|---------|
| Model 1: Crude | | |
| ICU-non-survivor (reference) | n.a. | n.a. |
| ICU-survivor* | −1.40 (−2.48; −0.50) | 0.004 |
| Interaction between group and timeb | −0.19 (−0.25; −0.12) | <0.001 |
| Model 2: Model 1 adjusted for age and sex | | |
| ICU-non-survivor (reference) | n.a. | n.a. |
| ICU-survivor* | −1.40 (−2.43; −0.37) | 0.009 |
| Interaction between group and timeb | −0.19 (−0.26; −0.12) | <0.001 |
| Model 3: Model 2 adjusted for obesity (BMI), diabetes mellitus, the presence of cardiovascular risk factors, chronic lung disease, liver disease, and chronic renal disease at baseline | | |
| ICU-non-survivor (reference) | n.a. | n.a. |
| ICU-survivor* | −1.40 (−3.05; −0.13) | 0.009 |
| Interaction between group and timeb | −0.19 (−0.26; −0.12) | <0.001 |
| Model 4: Model 3 additionally adjusted for APACHE II score | | |
| ICU-non-survivor (reference) | n.a. | n.a. |
| ICU-survivor* | −0.99 (−1.93; −0.06) | 0.038 |
| Interaction between group and timeb | −0.18 (−0.25; −0.12) | <0.001 |

n.a.: not applicable; CI: confidence interval; ICU: Intensive Care Unit; APACHE: Acute Physiology and Chronic Health Evaluation.

ICU-non-survivors as the reference category.

* A negative regression coefficient indicates that the average SOFA score of survivors is overall lower over time compared to the non-survivors.

b A negative regression coefficient for the interaction term indicates that the average SOFA score of survivors decreases more over time compared to the non-survivors. (i.e. the interaction between group and time models the change over time for both groups separately).
Adjustment for sex and age, and additionally for the presence of chronic lung disease, chronic liver disease and chronic renal disease, and obesity, diabetes mellitus, and cardiovascular risk factors, did not materially change the results (Table 3; Models 2 and 3). Additional adjustment for the APACHE II score reduced the negative regression coefficient that indicated the overall lower SOFA score over time (−0.99, 95% CI: −1.93; −0.06) for ICU-survivors compared to ICU-non-survivors, but the association remained significant. The improvement in SOFA score over time (−0.18, 95% CI: −0.25; −0.12) did not materially change (Table 3, Model 4).

We observed a significant interaction between sex and the association between groups over time (p = 0.043). After adjustment for age, compared to non-survivors, women survivors had a lower overall SOFA score during their ICU stay (−1.76, 95% CI: −3.36; −0.16) than men who survived (−1.19, 95% CI: −2.38; 0.01). Compared to non-survivors, women survivors had a larger decrease in SOFA score over time (−0.73, 95% CI: −1.05; −0.41) than men who survived (−0.16, 95% CI: −0.23; −0.09) (Table 3, Model 4).

Table 5 shows the organ component scores. The PaO2/FiO2 ratio was not associated with outcome. However, after adjustment for age and sex, ICU-survivors showed an overall higher PaO2 over time (0.78 kPa, 95% CI: 0.19; 1.38), and both an overall lower FiO2 need (−9.2%, 95% CI: −14.1; −4.3) and a lower FiO2 need slope over time (−0.59, 95% CI: −0.97; −0.21), as compared to ICU-non-survivors. After adjustment for age and sex, the SOFA cardiovascular component score did not differ between groups over time (−0.19 points, 95% CI: −0.70; 0.32), but the slope over time for ICU-survivors was lower compared to ICU-non-survivors (−0.09 points, 95% CI: −0.15; −0.03). After adjustment for age and sex, ICU-survivors showed both an overall lower SOFA renal component score (−0.83 points, 95% CI: −1.40; −0.26) and a lower SOFA renal component score slope over time (−0.05 points, 95% CI: −0.08; −0.02), as compared to ICU-non-survivors. Bilirubin, the Glasgow coma score and thrombocytes count, indicators for respectively, the liver, the central nervous system, and coagulation components, showed no association with survival.

Sensitivity analyses excluding 12 patients transferred for logistical reasons did not alter any of the conclusions.

4. Discussion

In this prospective cohort study including 93 mechanically ventilated participants with SARS-CoV-2 infection, we made five main observations. First, a decrease in SOFA score over time (which indicates improved organ function) is associated with ICU survival. Second, the association of the decrease in SOFA score with ICU survival remained present after adjustment for age, sex, the presence of chronic lung, renal and liver disease, obesity, diabetes mellitus, and cardiovascular risk factors, and after adjustment for the APACHE II score. Third, concerning the individual components of the SOFA score; the respiratory, circulatory, and renal organ components [35] appeared the most important drivers of the difference in trajectories of the SOFA score over time between ICU-survivors and ICU-non-survivors. The liver, the central nervous system, and coagulation components did not seem to play a role [36,37]. Fourth, the decrease in SOFA score over time between patients who survived the ICU vs. those that did not was statistically significantly greater for women (steeper slope) than men. Fifth, a higher admission SOFA score was not associated with ICU death.

Although previous studies report on SOFA score in COVID-19 [9-25,38], data on changes in SOFA score over time are sparse [15]. Shen C. et al. studied the role of convalescent plasma in five patients with SARS-CoV-2 infection and observed that treatment with plasma was associated with a decrease in SOFA score.[15] In our study, SOFA score on admission was not associated with outcome (7.3 points in survivors vs. 8.6 points vs non-survivors). Zhou F. et al. showed in a retrospective study of 191 patients that a higher SOFA score was associated with worse outcome (OR 5.65, 95%CI: 2.61–12.23) [14]. Maybe, in a general hospital population, SOFA score on admission is more indicative than in a selected population of patients admitted to the ICU [39].

The APACHE II score was primarily developed to rank disease severity between patients over the first 24 h of admission, whereas the SOFA score was developed to measure changes in disease severity.
over time [40]. The results show that in particular the difference in trajectories of SOFA score over time between ICU-survivors and ICU-non-survivors was independent of APACHE II score on admission. Furthermore, the SOFA score and APACHE II score on admission had a moderate correlation. Adjusting the association between SOFA score and outcome for APACHE II score appears odd as both scores identify disease severity of critical illness. This analysis, however, illustrates the fact that appropriate use of disease severity scores measuring alternative sources of variation (between patients vs. within patients) in multi-morbidity (i.e. both chronic multi-morbidity and acute multi-organ failure) is of utmost importance. The observation that trajectories of SOFA score are associated with outcome, independent of APACHE II score, could thus help to further refine the recent rapid guideline advice against the use of the SOFA score for ICU triage for patients with COVID-19 [41]. The present results, for example, add that appropriate SOFA score application in critical care, aids to identify patients with a favourable disease course [26,42,43].

This cohort study design has several strengths. First, the study is prospective by design and allows for many serial measurements over time in patients with SARS-CoV-2 infection. Second, systematic data collection is performed using a predefined protocol. Third, sensitivity analyses did not alter conclusions. A limitation of the study is the single centre approach and a relatively small sample size. However, the fast spread of the SARS-CoV-2 virus affects patients world-wide and urgently requires data to guide clinical decisions. Observations made in the Maastricht participants with SARS-CoV-2 may be generalised to other critically ill patients only. Nevertheless, including a heterogeneous sample of patients admitted to the ICU, without further exclusion criteria, reduced the chance of selection bias and contributes to the internal validity of the results for mechanically ventilated patients with SARS-CoV-2 infection. The SOFA score components use only a limited set of variables per organ component, and as weighting is applied to each component score, the overall SOFA score likely reflects pathophysiology of true multi-organ dysfunction suboptimally. Using a limited set of variables could have led to an underestimation of the reported association between multi-organ failure over the course of time and survival. Although multiple more sophisticated risk scores will be developed using traditional and artificial intelligence techniques, [44] SOFA score is widely known and easily applicable at the bedside. The latter features of the SOFA score are essential when resources are scarce, and time is of the essence in crises like the COVID-19 pandemic.

In summary: The outcome of patients with a SARS-CoV-2 infection admitted to the ICU is unfavourable for many. Admission characteristics seem insufficient to guide decisions about whether or not patients are likely to survive. This study revealed that temporal changes in multi-organ systems yield information that may guide decisions in individual mechanically ventilated patients with a SARS-CoV-2 infection [44]. The temporal change in SOFA score could be considered contributory to a decision to continue life-sustaining treatment or forgo life-sustaining support if considered futile. Caregivers can initiate adequate and timely end-of-life care and support. Furthermore, optimisation of care could have beneficial effects on caregivers and even the availability of beds for new patients in need of care. The extent of decrease in SOFA score during ICU admission that enables to predict outcome in mechanically ventilated patients with SARS-CoV-2 warrants further study in larger datasets [45].

5. Conclusions

Multi-organ involvement is a predominant characteristic of the SARS-CoV-2 infectious disease course in mechanically ventilated patients. A decrease in SOFA score over time, indicating improved organ function, is associated with ICU survival. The association between decreased SOFA score over time and survival was independent of comorbidities. Concerning the individual components of the SOFA score; the respiratory, circulatory, and renal organ components appeared most important. The results were more pronounced for women than men. Admission SOFA score was not associated with ICU death. These results suggest that SARS-CoV-2 infection can include multi-organ dysfunction that has a heterogeneous course with many dimensions. Serial SOFA scores may help guide optimisation of individual patients’ critical care in case of a second wave of the COVID-19 pandemic.

Ethics approval and consent to participate

The local institutional review board (Medisch Ethische Toetsingscomissie (METC) 2020–1565/ 300,523) of the Maastricht UMC+ approved the study, which was performed based on the regulations of Helsinki. During the pandemic, the board of directors of Maastricht UMC+ adopted a policy to inform patients and ask their consent to use the collected data and stored left-over serum samples for COVID-19 research purposes. The study is registered in the Netherlands Trial Register (registration number NL8613).

Consent for publication

Not applicable.

Availability of data and material

No concrete agreements on data sharing have been made yet. Before any data is shared outside the MUMC+, a datasharing plan will be drawn up in consultation with the data officer that conforms to relevant laws and regulations concerning personal data.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Authors’ contributions

IH and BB conceived and designed the study. JB, JT, RG, CG, RS, and SM contributed to data collection. SK, JB and BB analysed the data. JB, SK, CG, WM, IH, and BB drafted the manuscript. FT, JT, RG, RS, MA, MP, SM, and DB critically reviewed the manuscript. All authors read and approved the final manuscript.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2020.11.006.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Acknowledgements

We would like to thank all collaborators of Maastricht for their effort to support this study which is a joint-effort in a time when resources were already stressed maximally: Frank C. Bennis, Kirsten D.J. Bos, Moniek A. Donkers, Rald V.M. Groven, Nanon F.L. Heijnen, Ben J.M. Hermans, S.A.M. de Jongh, Marcel Koelmann, Johan van Koll, Mark M.G. Mulder, and Frank van Rosmalen.

References

[1]Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. Covid-19 does not lead to a “typical” acute respiratory distress syndrome. Am J Respir Crit Care Med 2020;201(10):1299–300.
[2]Arals YM, Murthy S, Webb S. COVID-19: a novel coronavirus and a novel challenge for critical care. Intensive Care Med 2020;46:833–4.
[3]Zhang J, Wang X, Jia X, Li J, Hu K, Chen G, et al. Risk factors for disease severity, unimprovement, and mortality of COVID-19 patients in Wuhan, China. Clin Microbiol Infect 2020;26:767–72.
[4] Organisation WH. Epidemiology: Q&A: similarities and differences - COVID-19 and influenza. viewed 16.04.2020 https://www.who.int/news-room/q-a-detail/q-a-similarities-and-differences-covid-19-and-influenza?lang=en

[5] Phua J, Weng L, Ling L, Egi M, Lim CM, Divatia JV, et al. Intensive care management of coronavirus disease 2019 (COVID-19): Challenges and recommendations. Lancet Respir Med 2020;8:506–17.

[6] Ioannidis JPA, Afxors C, Kontopoulou-Ioannidis DG. Population-level COVID-19 mortality risk for non-elderly individuals overall and for non-elderly individuals without underlying diseases in pandemic epicenters. Environ Res 2020;188:109890. https://doi.org/10.1016/j.envres.2020.109890.

[7] Klok FA, Kruij P, van der Meer NJM, Arbous MS, Gommers D, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;91:145–7.

[8] Madjd M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: A review. JAMA Cardiol 2020;5(7):831–40.

[9] Ferreira M, Bille T, Collercandy N, Szczypialk P, Dequin PF, Jouan Y, et al. Critically ill SARS-CoV-2-infected patients are not stratified by sex as the SPSO. Ann Intensive Care 2020;10(1):43.

[10] Ihle-Hansen H, Berge T, Tveita A, Ronning EJ, Erno PE, Andersen EL, et al. COVID-19: Experience from a Norwegian cohort of COVID-19 patients. Arch Environ Occup Health 2020;75:1620–6.

[11] Tang X, Du R, Wang R, Cao T, Guan L, Yang C, et al. Comparison of hospitalized patients with ARDS caused by COVID-19 and H1N1. Chest 2020;158:195–205.

[12] Wang D, Yin Y, Hu C, Liu X, Zhang X, Zhou S, et al. Clinical course and outcome of 107 patients infected with the novel coronavirus, SARS-CoV-2, discharged from two hospitals in Wuhan, China. Crit Care 2020;24(1):188.

[13] Wang D, Yin Y, Hu C, Liu X, Zhang X, Zhou S, et al. Clinical course and outcome of 107 patients infected with the novel coronavirus, SARS-CoV-2, discharged from two hospitals in Wuhan, China. Crit Care 2020;24(1):188.

[14] Yang Q, Wang P, Wang X, Qie G, Meng M, Tong X, et al. Retrospective study of risk factors for severe SARS-CoV-2 infections in hospitalized adult patients. Pol Arch Intern Med 2020;130(5):390–9.

[15] Zhou F, Yu T, Du R, Fan C, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet 2020;395(10229):1054–62.

[16] Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA 2020;323(16):1582–9.

[17] Pano S, Dalbeni A, Vettore E, Benfaredo D, Mattioli M, Gambino CG, et al. Abnormal liver function tests predict transfer to intensive care unit and death in COVID-19. Liver Int 2020;40(10):2394–406.

[18] Sar S, Lecoutrot A, Dosif M, Goldberg E, Bourbon C, Arnaud E, et al. The association of lung ultrasound images with COVID-19 infection in an emergency room cohort. Anaesthesia 2020;75:1620–5.

[19] Auld SC, Cardi-Scheibe M, Blum JM, Robichaux C, Kraft C, Jacob JT, et al. ICU and ventilator mortality among critically ill adults with coronavirus disease 2019. Critical Care Med 2020;48(9):e799–804 Online First.

[20] Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: A prospective cohort study. The Lancet 2020;395(10239):1763–70.

[21] Yu Y, Xu D, Fu S, Zhang J, Yang X, Xu L, et al. Patients with COVID-19 in 19 ICUs in Wuhan, China: A cross-sectional study. Crit Care 2020;24(1):219.

[22] Du RH, Liu YM, Yin W, Wang W, Guan L, Yuan ML, et al. Hospitalization and critical care of 109 decedents with COVID-19 pneumonia in Wuhan. China Ann Thorac Soc 2020;15(7):839–46.

[23] Wj Guan, Ni ZY, Hu Y, Liang W-h, Du C-q, He Jx, et al. Clinical characteristics of coronavirus disease 2019 in China. New Engl J Med 2020;382(18):1708–20.

[24] Su Y, Tu GW, Ju M, Su YJ, Zheng J, Ma GC, et al. Comparison of CRB-65 and quick sepsis-related organ failure assessment for predicting the need for intensive respiratory or vasopressor support in patients with COVID-19. J Infect 2020;81(4):647–79.

[25] Yang X, Yu Y, Xu J, Shu H, Xiao J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. Lancet Respir Med 2020;8(5):475–81.

[26] Zou X, Li S, Fang M, Hu M, Bian Y, Lang J, et al. Acute physiology and chronic health evaluation II score as a predictor of hospital mortality in patients of coronavirus disease 2019. Critical Care Med 2020;48(8):e567–65 Online First.