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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,j], Walther N.K.A. van Mook [a,i], Iwan C.C. van der Horst [a,j], Bas C.T. van Bussel [a,k,*]

[a] Department of Intensive Care, Maastricht University Medical Centre+, P. Debyelaan 25, 6202 AZ Maastricht, the Netherlands
[b] Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre+, Maastricht, the Netherlands
[c] Department of Cardiology, Maastricht University Medical Centre+, Maastricht, the Netherlands
[d] Department of Anaesthesiology and Pain Medicine, Maastricht University Medical Centre+, Maastricht, the Netherlands
[e] Department of Surgery, Maastricht University Medical Centre+, Maastricht, the Netherlands
[f] School of Nutrition and Translational Research in Metabolism (NUTRIM), Maastricht University, Universiteitssingel 40, 6229 ER Maastricht, the Netherlands
[g] School for Mental Health and Neuroscience (MHeNS), Maastricht University Medical Centre+, Maastricht, the Netherlands
[h] Department of Clinical Chemistry, Central Diagnostic Laboratory, Maastricht University Medical Centre+, Maastricht, the Netherlands
[i] School of Health Professions Education, Maastricht University, Universiteitssingel 60, 6229 ER Maastricht, the Netherlands
[j] Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Universiteitssingel 50, 6229 ER Maastricht, the Netherlands
[k] Care and Public Health Research Institute (CAPHRI), Maastricht University, Universiteitssingel 40, 6229 ER Maastricht, the Netherlands
[l] School for Oncology & Developmental Biology (GROW), Maastricht University, Universiteitssingel 40, 6229 ER Maastricht, the Netherlands

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ABSTRACT

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: 4–8) 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.

* Corresponding author at: Department of Intensive Care, Maastricht University Medical Centre+, P. Debyelaan 25, 6202 AZ Maastricht, the Netherlands.
E-mail addresses: julia.bels@mumc.nl (J.L.M. Bels), sander.van.kuijk@mumc.nl (S.M.J. van Kuijk), chahinda.ghossein@mumc.nl (C. Ghossein-Doha), fabian.tijssen@mumc.nl (F.H. Tijssen), r.vangassel@maastrichtuniversity.nl (R.J.J. van Gassel), jeanette.tas@mumc.nl (J. Tas), r.schnabel@mumc.nl (R.M. Schnabel), marcel.aries@mumc.nl (M.J.H. Aries), marcel.vande.poll@mumc.nl (M.C.G. van de Poll), d.bergmans@mumc.nl (D.C.J.J. Bergmans), steven.meex@mumc.nl (S.J.R. Meex), w.van.mook@mumc.nl (W.N.K.A. van Mook), iwan.vander.horst@mumc.nl (I.C.C. van der Horst), bas.van.bussel@mumc.nl (B.C.T. van Bussel).

List of abbreviations

APACHE II	Acute Physiology and Chronic Health Evaluation II
BMI	Body Mass Index
CI	Confidence interval
CORADS	COVID-19 Reporting and Data system
FiO_2	Fraction of inspired oxygen
GCS	Glasgow Coma Scale

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ICU	Intensive Care Unit
IQR	Interquartile range
LOS	Length of stay
MaastrICCht	Maastricht Intensive Care Cohort
Maastricht UMC	Maastricht Universitair Medisch Centrum
MAP	Mean arterial pressure
METc	Medisch Ethische Toetsingscomissie
n.a.	Not applicable/available
n.s.	Not specified
OR	Odds ratio
PaO_2	Partial pressure of oxygen
PCR	Polymerase chain reaction
qSOFA	Quick SOFA
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SOFA	Sequential Organ Failure Assessment

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 stepwise 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/m^2), 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

Table 1
Overview of available literature on SOFA score in COVID-19 patients.

Author	Country	n	Design	ICU only	ICU patients	Primary outcome	Admission SOFA score		Uni- or multivariate	Consent	Additional comments
							Survivors	Non-survivors			
Ihle-Hansen, H.	Norway	42	Retrospective cohort	No	9 (21%)	Descriptives general	No	No	n.a.	Waived	Only three components qSOFA score
Wang, D.	China	107	Retrospective cohort	No	n.s.	Hospital mortality	No	No	n.a.	Yes	Only three components of SOFA score
Ferreira, M.	France	52	Retrospective cohort	Yes	52 (100%)	Descriptives qSOFA	No	No	n.a.	Waived	Only three components qSOFA score
Yao, Q.	China	108	Retrospective cohort	No	17 (16%)	Hospital mortality	Yes	Yes	Multivariate	Waived	Admission SOFA associated with hospital mortality (OR 2.4, 1.3–4.4, $p = 0.004$)
Ling, L.	China	8	Retrospective cohort	Yes	8 (100%)	7 days SOFA scores 28-day mortality	Yes	Yes	n.a.	n.s.	No associations studied or reported
Tang, X.	China	73	Retrospective case–control	No	14 (19%)	Discharge, mortality, LOS	Yes	Yes	Multivariate	Waived	Compared COVID-19 and influenza A
Zhou, F.	China	191	Retrospective cohort	No	50 (26%)	Hospital mortality	Yes	Yes	Multivariate	Waived	Admission SOFA associated with hospital mortality (OR 5.7, CI 2.6–12.2, $p < 0.0001$)
Shen, C.	China	5	Uncontrolled case series	Yes	5 (100%)	Descriptives serial SOFA score	No	No	n.a.	Yes	SOFA score decreased over 12 days after convalescent plasma administration
Zhang, G.	China	221	Retrospective cohort	No	44 (20%)	Hospital mortality	Yes	Yes	n.a.	Waived	SOFA score was lower in 23 ICU-survivors than 9 ICU-non-survivors, $p = 0.009$
Piano, S.	Italy	565	Retrospective cohort	No	83 (15%)	Hospital mortality, transfer to ICU	No	No	n.a.	Yes	Composite outcome of death or ICU admission was used
Bar, S.	France	31	Prospective cohort	No	8 (26%)	Lung ultrasound COVID-19 diagnosis	No	No	n.a.	Yes	Only three components qSOFA score
Auld, S.	USA	217	Retrospective cohort	Yes	217 (100%)	Hospital mortality	Yes	Yes	n.a.	n.s.	No associations studied or reported
Cummings, M.	USA	257	Prospective cohort	No	n.s.	Hospital mortality	No	No	n.a.	Waived	SOFA at ICU admission obtained in 86% of study population (11 (8–13))
Yu, Y.	China	226	Cross-sectional	Yes	226 (100%)	Descriptives general	No	No	n.a.	Waived	SOFA at ICU admission obtained in 85% of study population (4 (2–8))
Su, Y.	China	116	Retrospective cohort	No	n.s.	Respiratory or vasopressor support	No	No	n.a.	n.s.	Only three components qSOFA score
Zou, X.	China	154	Retrospective cohort	Yes	154 (100%)	Hospital mortality	Yes	Yes	Multivariate	n.s.	Admission SOFA associated with hospital mortality (adjusted HR, 1.43; 95% CI, 1.26–1.62)
Du, R-H.	China	109	Retrospective cohort	No	51 (47%)	Descriptives general	No	No	n.a.	Waived	Results not stratified by survival outcome
Guan, W.	China	1099	Retrospective cohort	No	55 (5%)	ICU admission, mechanical ventilation, mortality	No	No	n.a.	Waived	Only some components of SOFA score
Yang, X.	China	52	Retrospective cohort	Yes	52 (100%)	28-day mortality	Yes	Yes	n.a.	Waived	No associations studied or reported

Search performed until June 15, 2020 in PubMed and Google Scholar. Search terms "COVID-19", "ICU", "intensive care", "SOFA", and "Sequential Organ Failure Assessment". SOFA, Sequential Organ Failure Assessment; ICU, Intensive Care Unit; n.a., not available; n.s., not specified; LOS, length of stay. SOFA score: Respiratory system was scored 0 if $PaO_2/FiO_2 \geq 53.3$ kPa, 1 if $PaO_2/FiO_2 < 53.3$ kPa, 2 if $PaO_2/FiO_2 < 40$ kPa, 3 if $PaO_2/FiO_2 < 26.7$ kPa with respiratory support and 4 if $PaO_2/FiO_2 < 13.3$ kPa with respiratory support. Coagulation system was scored 0 if platelets $\geq 150 \times 10^3$ μL^{-1}, 1 if platelets $< 150 \times 10^3$ μL^{-1}, 2 if platelets $< 100 \times 10^3$ μL^{-1}, 3 if platelets $< 50 \times 10^3$ μL^{-1} or 4 if platelets $< 20 \times 10^3$ μL^{-1}. Liver system was scored 0 if bilirubin < 20 μmol L^{-1}, 1 if bilirubin 20–32 μmol L^{-1}, 2 if bilirubin 33–101 μmol L^{-1}, 3 if bilirubin 102–204 μmol L^{-1} and 4 if bilirubin > 204 μmol L^{-1}. Cardiovascular system was scored 0 if mean arterial pressure (MAP) ≥70 mmHg, 1 if MAP <70 mmHg, 2 if dobutamine (any dose) or dopamine $< 5 \mu g kg^{-1} min^{-1}$ for at least 1h, 3 if epinephrine ≤ 0.1 $\mu g kg^{-1} min^{-1}$ or norepinephrine ≤ 0.1 $\mu g kg^{-1} min^{-1}$ or dopamine 5.1-15 $\mu g kg - 1 min^{-1}$ for at least 1 h, 4 if epinephrine > 0.1 $\mu g kg^{-1} min^{-1}$ or norepinephrine > 0.1 $\mu g kg^{-1} min^{-1}$ or dopamine > 15 $\mu g kg^{-1} min^{-1}$ for at least 1 h. Central nervous system was scored 0 if Glasgow coma score (GCS) was 15, 1 if GCS was 13–14, 2 if GCS was 10–12, 3 if GCS was 6–9, and 4 if GCS was <6. In sedated patients, admission GCS was used. Renal component was scored 0 if creatinine < 110 μmol L^{-1}, 1 if creatinine 110–170 μmol L^{-1}, 2 if creatinine 171–299 μmol L^{-1}, 3 if creatinine 300–440 μmol L^{-1} or urine output <500 ml per day, 4 if creatinine > 440 μmol L^{-1} or urine output <200 ml per day.

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 polynomials of time. Using the Akaike Information Criterion, the best fitting 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

Table 2
ICU admission demographic characteristics, medical history, cardiorespiratory indices, and risk indicators in ICU-survivors and ICU-non-survivors.

	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[a]	19 (9; 33)	14 (3; 17)	0.004[c]
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/m^2	27.9 (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%)	1.000[b]
Chronic lung disease	4 (7%)	4 (11%)	0.469[b]
Chronic renal disease	1 (2%)	1 (3%)	1.000[b]
Diabetes mellitus type 2	7 (12%)	7 (20%)	0.300
Presence of any cardiovascular risk factor (i.e. hypertension, dyslipidaemia, smoking, obesity)	24 (41%)	21 (60%)	0.082
APACHE II score, points	15.0 (4.9)	18.0 (6.1)	0.030
SOFA score, points	7.3 (1.9)	8.6 (2.8)	0.068
Mechanical ventilation, yes	58 (100%)	35 (100%)	–
FiO_2, %	71.9 (19.3)	77.7 (18.8)	0.256
Respiration rate, per minute (highest in first 24 h)	27.9 (7.7)	26.5 (6.1)	0.438
Inspiratory pressure, cm H_2O	26.8 (4.5)	27.0 (3.7)	0.861
Positive end-expiratory pressure, cm H_2O	14.0 (2.2)	14.5 (2.6)	0.608
Tidal volume, ml	467.1 (62.3)	454.9 (87.6)	0.641
Arterial blood gas pO_2, kPa	11.1 (4.5)	10.9 (3.9)	0.826
Arterial blood gas pCO_2, kPa	5.5 (1.5)	5.8 (1.7)	0.425
Arterial blood gas pH	7.3 (0.1)	7.3 (0.1)	0.146
Mean arterial pressure, mmHg (lowest in first 24 h)	64.1 (10.2)	66.0 (12.0)	0.505
Bilirubin, μg/l[a]	9.4 (6.7; 12.5)	10.0 (6.1; 19.4)	0.453[c]
Dialysis, yes	0 (0%)	0 (0%)	1.000
Creatinine, μmol/l[a]	75.0 (59.5; 97.0)	104.0 (68.0; 165.0)	0.018[c]
Urine production, ml/24 h[a]	1090.0 (736.3; 1366.3)	902.5 (445.0; 1345.0)	0.252[c]
Glasgow coma score	14.6 (2.0)	14.3 (2.5)	0.626
Thrombocytes, 10E^9/l	270.2 (110.5)	279.1 (110.5)	0.784

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.
[a] Median and 1st and 3rd quartiles.
[b] Fisher's Exact test.
[c] Mann Whitney *U* test.

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 *between* 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.

The mean SOFA score at baseline was 7.3 for eventual ICU-survivors (SD: 1.9) compared to 8.6 (SD: 2.8) for those who eventually died in

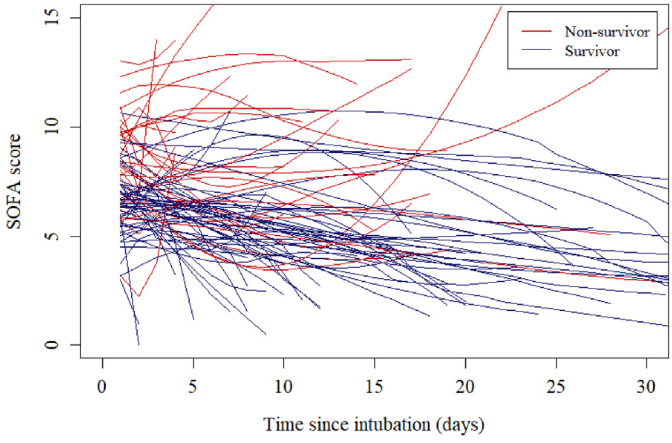

Fig. 1. SOFA scores over time in ICU-survivors and ICU-non-survivors. A lower SOFA score indicates less organ dysfunction.

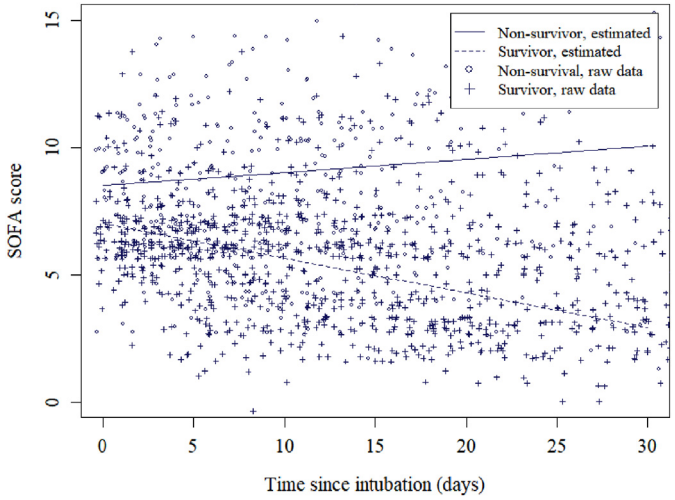

Fig. 2. Observed and predicted SOFA scores over time for ICU-survivors and in ICU-non-survivors. A lower SOFA score indicates less organ dysfunction. Note that some jitter has been applied to the raw data to make multiple observations with the same values visible.

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

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[a]	−1.49 (−2.48; −0.50)	0.004
Interaction between group and time[b]	−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[a]	−1.40 (−2.43; −0.37)	0.009
Interaction between group and time[b]	−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[a]	−1.40 (−3.05; −0.13)	0.009
Interaction between group and time[b]	−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[a]	−0.99 (−1.93; −0.06)	0.038
Interaction between group and time[b]	−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] 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).

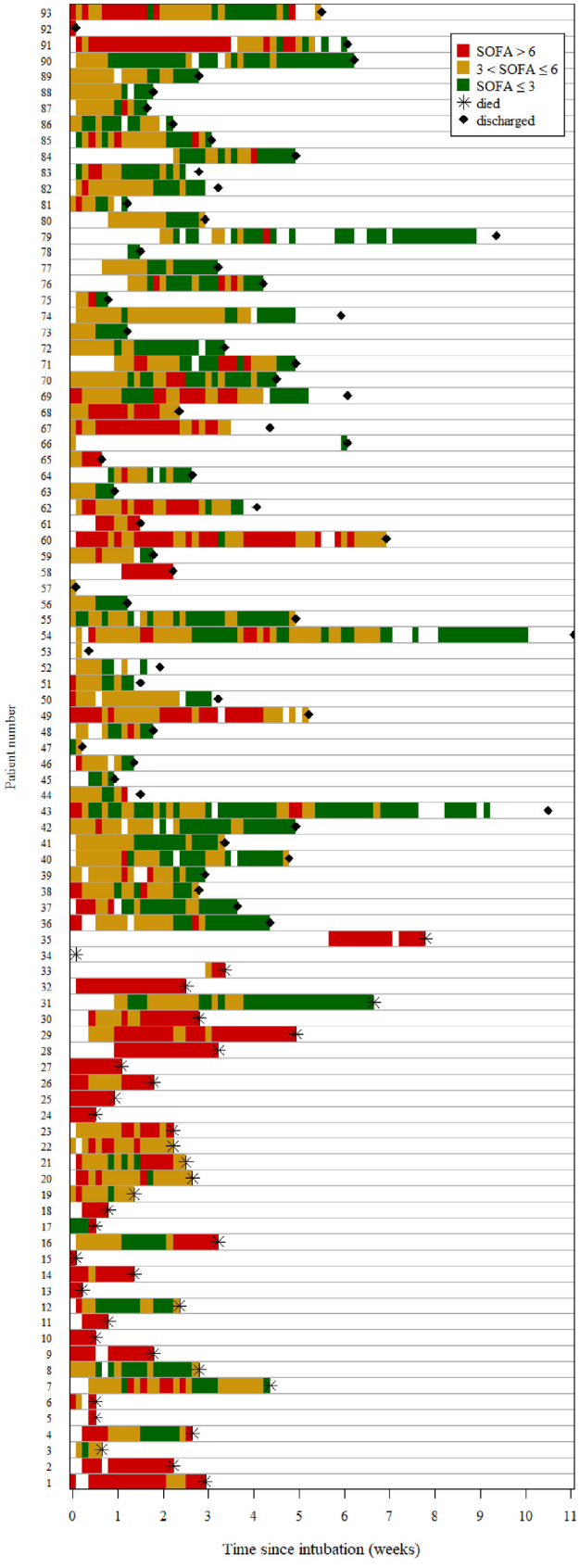

Fig. 3. Development of categories of SOFA scores over weeks in ICU-survivors and in ICU-non-survivors. A lower SOFA score indicates less organ dysfunction.

of SOFA scores over weeks per participant for those who survived the ICU, and those who did not survive.

Table 4
Results of linear mixed-effect models: difference in SOFA score development; stratified by sex, adjusted for age.

Stratified by sex	Men		Women	
	Regression coefficient (95% CI)	p-value	Regression coefficient (95% CI)	p-value
ICU-non-survivor	n.a.	n.a.	n.a.	n.a.
ICU-survivor[a]	−1.19 (−2.38; 0.01)	0.052	−1.76 (−3.36; −0.16)	0.035
Interaction between group and time[b]	−0.16 (−0.23; −0.09)	<0.001	−0.73 (−1.05; −0.41)	<0.001

n.a.: not applicable; CI: confidence interval; ICU: intensive care unit.
ICU-non-survivors as the reference category.
The sample size for each of the analyses is reduced to 73 for the analyses for men and 20 for women.
[a] 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 SOFA score over time and ICU mortality ($p = 0.043$). 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 4).

Table 5 shows the organ component scores. The PaO_2/FiO_2 ratio was not associated with outcome. However, after adjustment for age and sex, ICU-survivors showed an overall higher PaO_2 over time (0.78 kPa, 95% CI: 0.19; 1.38), and both an overall lower FiO_2 need (−9.2%, 95% CI: −14.1; −4.3) and a lower FiO_2 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

Table 5
Results of linear mixed-effect models: development of components of SOFA score; adjusted for age and sex.

	Adjusted regression coefficient (95% CI)	p-value	Adjusted interaction (95% CI)	p-value
PaO_2/FiO_2 ratio	0.07 (−0.02; 0.16)	0.140	0.00 (0.00; 0.00)	0.625
PaO_2, kPa	0.78 (0.19; 1.38)	0.011	0.01 (−0.02; 0.04)	0.447
FiO_2, %	−9.18 (−14.06; −4.31)	<0.001	−0.59 (−0.97; −0.21)	0.002
SOFA cardiovascular component score	−0.19 (−0.70; 0.32)	0.462	−0.09 (−0.15; −0.03)	0.002
Bilirubin, μmol/l	1.44 (−3.48; 6.35)	0.564	−0.47 (−1.55; 0.61)	0.396
SOFA renal component score	−0.83 (−1.40; −0.26)	0.005	−0.05 (−0.08; −0.02)	0.002
Glasgow coma score	−0.76 (−1.80; 0.28)	0.151	−0.01 (−0.05; 0.03)	0.751
Thrombocytes, $10E^9$/l	26.5 (−4.49; 57.55)	0.093	−1.00 (−4.48; 2.47)	0.572

ICU-non-survivors as the reference category.

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 *MaastrICCht* 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.

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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.

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Declaration of Competing Interest

The authors declare that they have no competing interests.

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