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RESEARCH ARTICLE

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Association between days alive without life support/out of hospital and health-related quality of life

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Abstract

Background: Trials in critically ill patients increasingly focus on days alive without life support (DAWOLS) or days alive out of hospital (DAOOH) and health-related quality of life (HRQoL). DAWOLS and DAOOH convey more information than mortality and are simpler and faster to collect than HRQoL. However, whether these outcomes are associated with HRQoL is uncertain. We thus aimed to assess the associations between DAWOLS and DAOOH and long-term HRQoL.

Methods: Secondary analysis of the COVID STEROID 2 trial including adults with COVID-19 and severe hypoxaemia and the Handling Oxygenation Targets in the Intensive Care Unit (HOT-ICU) trial including adult intensive care unit patients with acute hypoxaemic respiratory failure. Associations between DAWOLS and DAOOH at day 28 and 90 and long-term HRQoL (after 6 or 12 months) using the EuroQol 5-dimension 5-level survey (EQ VAS and EQ-5D-5L index values) were assessed using flexible models and evaluated using measures of fit and prediction adequacy in both datasets (comprising internal performance and external validation), non-parametric correlation coefficients and graphical presentations.

Results: We found no strong associations between DAWOLS or DAOOH and HRQoL in survivors at HRQoL-follow-up (615 and 1476 patients, respectively). There was substantial variability in outcomes, and predictions from the best fitted models were poor both internally and externally in the other trial dataset, which also showed

inadequate calibration. Moderate associations were found when including non-survivors, although predictions remained uncertain and calibration inadequate.

Conclusion: DAWOLS and DAOOH were poorly associated with HRQoL in adult survivors of severe or critical illness included in the COVID STEROID 2 and HOT-ICU trials.

KEYWORDS

critical care, days alive out of hospital, days alive without life support, health-related quality of life, outcome selection

Editorial Comment

More patient-centred outcomes are preferred in current ICU treatment trials, including days alive without life support or days outside of hospital, as well as health-related quality of life. The results from two recent trials were assessed for associations between these outcomes. The two first number of days with the good outcomes were not associated with the later quality of life scoring for survivors in these two cohorts.

1 | INTRODUCTION

All-cause mortality is highly patient-important and frequently used as the primary outcome in randomised clinical trials (RCTs) in the critical care setting[1,2] despite several limitations,[1,3,4] including the need for larger samples than for non-dichotomous outcomes.[5] Consequently, critical care RCTs are often only powered to detect mortality differences substantially larger than what could be considered clinically important or plausible.[1,6,7]

Furthermore, survivors of critical illness survive to very different health states, which are quantifiable using other outcomes such as health-related quality of life (HRQoL). HRQoL is highly patient-important and increasingly used in critical care RCTs as a secondary, long-term outcome.[2] However, HRQoL comes with limitations, including handling of non-survivors (focusing on survivors only may yield substantially misleading results[8]) and loss to follow-up (which may be related to the actual HRQoL[9]). Finally, long follow-up durations may be an additional disadvantage in emergency situations (e.g., pandemics) or if used to guide adaptation in adaptive trials.[10]

Days alive without life support (DAWOLS) and days alive out of hospital (DAOOH) convey more information than mortality[5] and can be considered as composites of mortality and illness durations and severity, which may be hypothesised to be associated with long-term HRQoL.[11] These outcomes have increasingly been used as primary outcomes during the coronavirus disease 2019 (COVID-19) pandemic,[12,13] and similar outcomes have previously been validated in surgical patients where fewer days at home were found to be associated with an increased number of post-operative complications.[14] Although these outcomes also have limitations,[3,15,16] they are objective, easy to register and generally assessed after short-to-medium follow-up durations, all making them less prone to missing data compared with HRQoL. In this study, we assessed the associations between DAWOLS and DAOOH and long-term HRQoL in two large, international RCTs in severely and critically ill adults.

2 | METHODS

This study was conducted according to a protocol and statistical analysis plan published prior to the conduct of the analysis and before HRQoL-follow-up was completed for one of the included trials.[11,17,18] This manuscript was prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist[19] (Data S1).

2.1 | Population and data sources

We included severely and critically ill adults enrolled in two investigator-initiated, international RCTs:

The COVID STEROID 2 trial (ClinicalTrials.gov: NCT04509973; approved by the Committees on Health Research Ethics in the Capital Region of Denmark [H-20051056] on 18 August 2020) randomised 1000 adults with COVID-19 and severe hypoxaemia to dexamethasone 12 mg versus 6 mg daily for up to 10 days. Enrolment took place in 31 intensive care units (ICUs) and medical wards in Denmark, India, Sweden and Switzerland between 27 August 2020 and 20 May 2021.[12]

The Handling Oxygenation Targets in the Intensive Care Unit (HOT-ICU) trial (ClinicalTrials.gov: NCT03174002; approved by the North Denmark Region Committee on Health Research Ethics [N-20170015] on 22 May 2017) randomised 2928 adult ICU patients with acute hypoxaemic respiratory failure to an arterial partial pressure of oxygen target of 8 kPa versus 12 kPa during the ICU stay for up to 90 days. Enrolment took place in 35 ICUs in Denmark, Switzerland, Finland, the Netherlands, Norway, the United Kingdom and Iceland between 17 June 2017 and 3 August 2020.[20]

Both trials were conducted in accordance with the Declaration of Helsinki with enrolment after informed consent by patients or their legal surrogates; additional details on consent procedures and

approvals are available elsewhere.[12,20–22] No further approvals were required for this secondary study.

2.2 | Outcomes

This study assessed the following outcomes:

1. Days alive without life support (DAWOLS)
2. Days alive out of hospital (DAOOH)
3. EuroQol visual analogue scale (EQ VAS) values[23]
4. EuroQol 5-dimension, 5-level (EQ-5D-5L) index values[23]
5. All-cause mortality

Complete definitions are included in Data S1, including descriptions of slight differences in definitions between the two trials and calculations based on partially complete data for one outcome in a subset of patients in the HOT-ICU trial.

DAWOLS and DAOOH were assessed 28 and 90 days after randomisation; HRQoL (EQ VAS and EQ-5D-5L index values) after 6 months (COVID STEROID 2 trial) or 12 months (HOT-ICU trial); mortality after 28 and 90 days and at the time of HRQoL-follow-up.

HRQoL was assessed by either phone or mail[12,17,18,20–22] using the EQ-5D-5L survey[23] consisting of EQ VAS and five HRQoL domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression; five levels each) used to calculate EQ-5D-5L index values.

EQ VAS scores range from 0 to 100 (worst to best imaginable health states, respectively), while EQ-5D-5L index values are calculated using previously derived country-specific value sets[23] based on studies conducted by interviewing representative samples asked to 'weigh' different health states defined by different responses to the five individual domains. EQ-5D-5L index values are anchored at 1 (perfect health) and 0 (a health state considered as bad as being dead) with negative values corresponding to health states considered worse than death.[23] As recommended,[24] we primarily calculated index values using national value sets where available (Denmark, India, the United Kingdom [England], the Netherlands and Sweden[25–29]) and using the Danish value set for the remaining European countries.[11]

2.3 | Statistical analyses

Analyses were conducted separately in the two trial databases using R v. 4.1.0 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) with the *tidyverse* and *mice* packages.

Descriptive baseline and outcome data were calculated for all patients and stratified by survival/respondence status at HRQoL-follow-up. Numeric data were summarised using medians with interquartile ranges (IQRs), and categorical data were summarised using absolute and relative frequencies.

2.3.1 | Primary analyses

The primary analyses were conducted in patients known to be alive at HRQoL-follow-up only and assessed all combinations of DAWOLS or DAOOH (at both time points) and EQ VAS or EQ-5D-5L index values. The associations were modelled using the best fitting (lowest root mean squared error [RMSE]) first- or second-degree fractional polynomial transformations[30] as described in detail in the protocol[11] and Data S1. We present the full model fits for the selected models and evaluated fit using RMSEs and Spearman's non-parametric rank correlation coefficient with 95% confidence intervals (CIs) in the trial dataset used to fit each model. Models were assessed externally in the other trial dataset using RMSEs, calibration-in-the-large (mean prediction error; ideally 0, values >0 indicate systematic over-prediction, while values <0 indicate systematic under-prediction) and calibration slopes (systematic over-/underfitting; ideally 1, values <1 suggest too extreme predictions, while values >1 suggest too moderate predictions).[31] Finally, best fits from both datasets were visualised as curves with 95% confidence bands overlaid scatterplots of each trial dataset.

2.3.2 | Secondary analyses

The distributions of DAWOLS and DAOOH (at both time points) according to each level of each EQ-5D-5L dimension were assessed numerically (medians with IQRs) and graphically in both datasets.

2.3.3 | Sensitivity analyses

Three sets of pre-specified[11] sensitivity analyses were conducted for the primary analyses.

First, all patients were included, with EQ VAS and EQ-5D-5L index values set to 0 (the lowest possible value for EQ VAS and the value that corresponds to a health state as bad as being dead, respectively) in non-survivors at HRQoL-follow-up. Patients who died before DAWOLS–DAOOH follow-up were assigned 0 days (worst possible value) for these outcomes as previously recommended and frequently done in trials to make death the worst possible outcome in the analyses.[15,32]

Of note, to focus on patients where the prediction of HRQoL based on DAWOLS or DAOOH is most difficult, we focused on survivors only in the primary analyses, as the assignment of specific, fixed values to non-survivors for HRQoL values was expected to lead to stronger associations as mortality also affects the DAWOLS–DAOOH outcomes. As we only focused on associations between outcomes in the complete trial populations (i.e., not separated by allocation), we consider this the most appropriate approach for the primary analyses in this study and supplemented it with the sensitivity analyses including non-survivors. This may be in contrast with the optimal analysis of treatment effects on HRQoL in trials conducted in populations with high mortality where treatments are hypothesised to affect mortality. In such cases, focusing on survivors only may be misleading,[8] as treatments that improve survival are likely to lead to more of the most ill

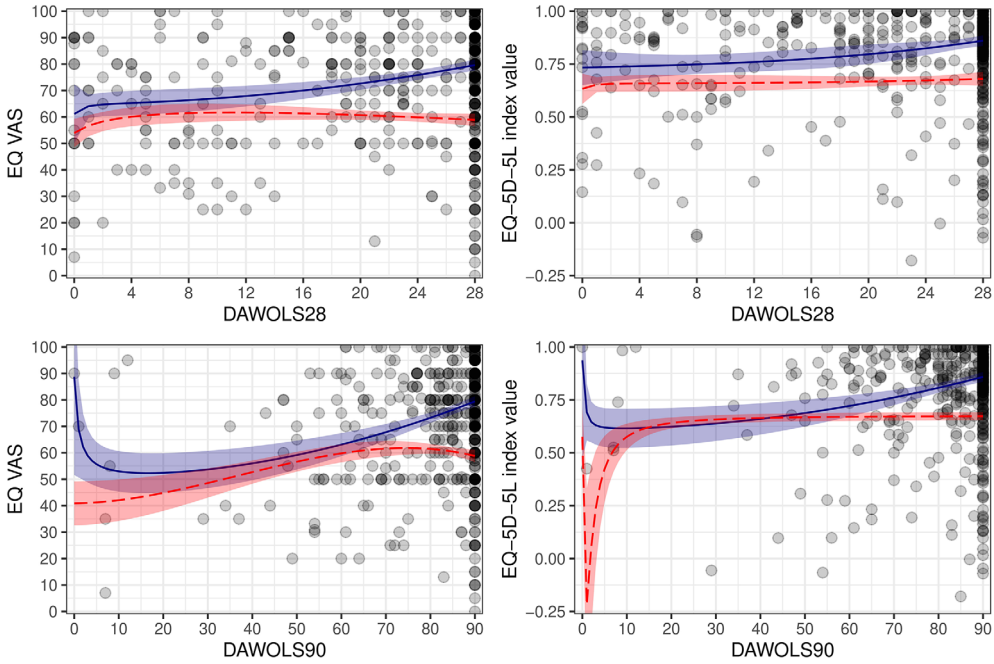

FIGURE 1 Associations between DAWOLS and HRQoL in survivors only the COVID STEROID 2 trial. Scatter plots with the data from the COVID STEROID 2 trial using the multiply imputed datasets (survivors only, using mean values across all imputations); darker points indicate more patients with identical values. DAWOLS after 28 and 90 days are presented on the horizontal axes, while HRQoL values (EQ VAS or EQ-5D-5L index values) are presented on the vertical axes. The predicted values according to the best fitting fractional polynomial transformation models from both trials are presented with 95% confidence bands; predictions based on the best model from the COVID STEROID 2 trial are presented in blue with full lines, while predictions based on the best model from the HOT-ICU trial are presented in red with dashed lines (external validation). DAWOLS28/90, days alive without life support after 28 or 90 days; EQ-5D-5L, EuroQol 5-dimension 5-level survey; EQ VAS, EuroQol visual analogue scale; HRQoL, health-related quality of life.

patients surviving, who, in turn, are prone to have relatively low HRQoL, causing potentially beneficial treatments to appear inferior. Second, all patients were included, with the actual DAWOLS-DAOOH values used (i.e., no penalisation of death). Third, sensitivity analyses were conducted using EQ-5D-5L values calculated using the Danish value set[25] for all patients as most patients were included in Denmark.

Fourth, a post hoc sensitivity analysis was conducted for DAOOH after 28 days, excluding 402 HOT-ICU patients whose exact number of days were unobtainable from the available data; for the other analyses, values from these patients were multiply imputed and truncated to the possible range of values as described in Data S1.

2.4 | Sample size

The sample size was fixed to the relevant intention-to-treat populations from the COVID STEROID 2 and HOT-ICU trials, that is, 982 patients (615 survivors at HRQoL-follow-up) and 2910 patients (1476 survivors at HRQoL-follow-up), respectively.[12,17,18,20] Consequently, formal sample size calculation was forgone.[11]

2.5 | Missing data

The proportion of missingness for all variables is presented; as patients with missing data for at least one outcome exceeded 5% in both trials, we used multiple imputation[33] with 25 imputed datasets for each trial as specified in the protocol[11] and detailed in Data S1.

3 | RESULTS

Descriptive baseline and outcome data are presented in Table S1 for the COVID STEROID 2 trial and Table S2 for the HOT-ICU trial. In both trials, patients who died before HRQoL-follow-up were older, received more life support at baseline and had more co-morbidities than those alive; HRQoL respondents and non-respondents were similar at baseline and for DAWOLS and DAOOH outcomes, while imputed HRQoL values were somewhat lower in non-respondents than observed values in respondents in both trials.

3.1 | Associations between DAWOLS or DAOOH and HRQoL in survivors (primary analyses)

In total, 615 (62.6%) of the included patients in COVID STEROID 2 and 1476 (50.7%) of the included patients in HOT-ICU were alive at HRQoL-follow-up and included in the primary analyses assessing the associations between DAWOLS or DAOOH at both time points and HRQoL in survivors. Associations between all outcomes including the best model fits in both trials are visualised in Figures 1–4; there were

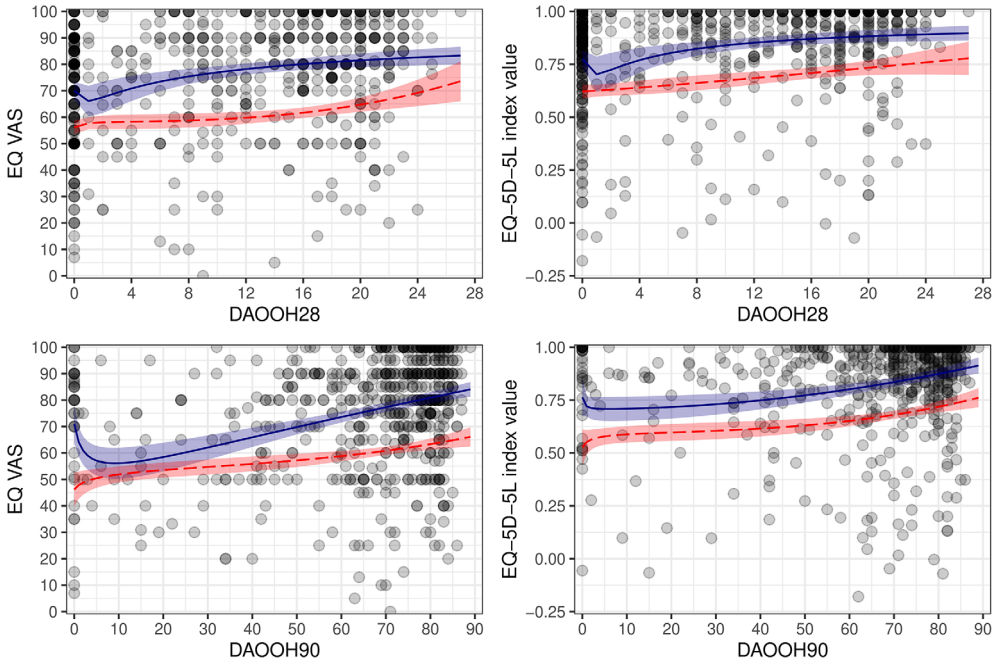

FIGURE 2 Associations between DAOOH and HRQoL in survivors only the COVID STEROID 2 trial. Scatter plots with data from the COVID STEROID 2 trial using the multiply imputed datasets (survivors only, using mean values across all imputations); darker points indicate more patients with identical values. DAOOH after 28 and 90 days are presented on the horizontal axes, while HRQoL values (EQ VAS or EQ-5D-5L index values) are presented on the vertical axes. The predicted values according to the best fitting fractional polynomial transformation models from both trials are presented with 95% confidence bands; predictions based on the best model from the COVID STEROID 2 trial are presented in blue with full lines, while predictions based on the best model from the HOT-ICU trial are presented in red with dashed lines (external validation). DAOOH28/90, days alive out of hospital after 28 or 90 days; EQ-5D-5L, EuroQol 5-dimension 5-level survey; EQ VAS, EuroQol visual analogue scale; HRQoL, health-related quality of life.

substantial scatter in all distributions without visual indications of consequential associations for most combinations of DAWOLS or DAOOH and HRQoL.

Performance measures are presented in Table 1; in the COVID STEROID 2 trial, Spearman's correlation coefficients were between 0.24 and 0.28 with 95% CIs compatible with increases in HRQoL with increased DAWOLS and DAOOH for all associations. In the HOT-ICU trial, Spearman's correlation coefficients were close to 0 for all DAWOLS outcomes and HRQoL with 95% CIs compatible with both increases and decreases or no association for all DAWOLS- and HRQoL-combinations. For DAOOH-HRQoL associations in HOT-ICU trial, Spearman's correlation coefficients were between 0.12 and 0.17 with 95% CIs compatible with increases in HRQoL with increased DAOOH. RMSE were relatively high both internally and externally (in the alternate dataset); calibration-in-the-large indicated systematic over-prediction when using the models fit to COVID STEROID 2 to predict values in HOT-ICU and systematic under-prediction when using the models fit to HOT-ICU to predict values in COVID STEROID 2. Calibration slopes when assessing COVID STEROID 2-based predictions in the HOT-ICU data were on both sides of 1 indicating either too extreme or too moderate predictions for different model fits; for the HOT-ICU-based predictions in the COVID STEROID 2 data, all calibration slopes were <1 indicating too extreme predictions for all combinations of DAWOLS–DAOOH and HRQoL assessed. Complete fits of the selected models for all associations are presented in Tables S3 and S4.

3.2 | Distributions of DAWOLS or DAOOH according to EQ-5D-5L domain values (secondary analyses)

The distributions of DAWOLS–DAAOH according to the values in the different EQ-5D-5L domains in both datasets are presented in Tables S5 and S6 and Figures S1 andS2. In both trials, patients with worse EQ-5D-5L domain scores generally had fewer DAWOLS or DAOOH at both follow-up time points.

3.3 | Sensitivity analyses

The results from all sensitivity analyses are presented in Tables S7–-S11 and Figures S3–S10. The two sets of sensitivity analyses that included non-survivors and assigned these patients 0 or the actual values for DAWOLS and DAOOH, respectively, showed moderate associations (increasing HRQoL with increasing DAWOLS or DAOOH; higher correlation coefficients) but still relatively high RMSEs and poor calibration, when assessed in the alternate dataset. The results

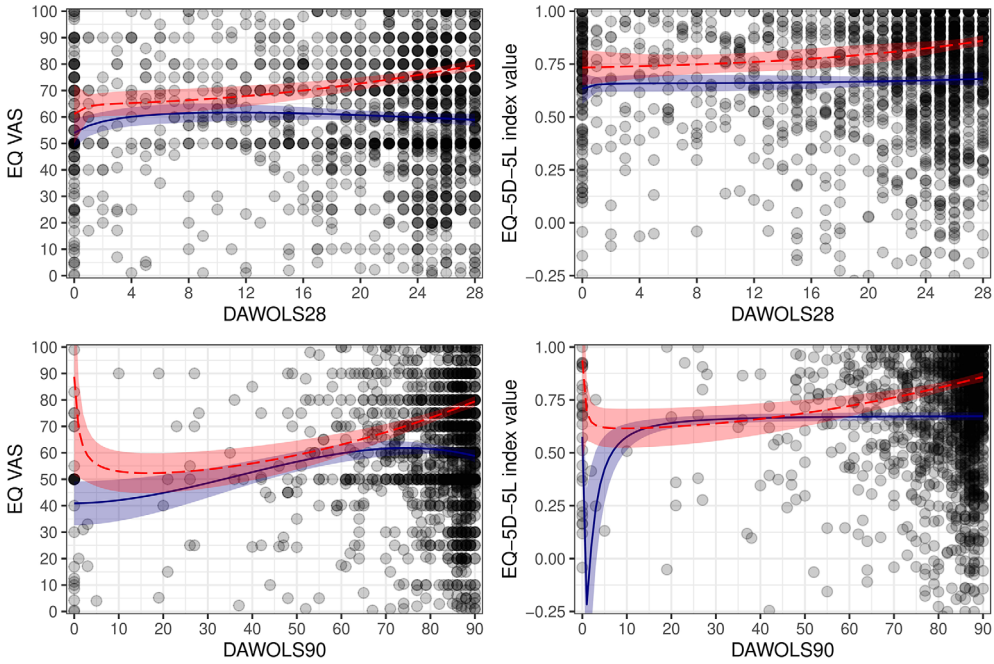

FIGURE 3 Associations between DAWOLS and HRQoL in survivors only the HOT-ICU trial. Scatter plots with data from the HOT-ICU trial using the multiply imputed datasets (survivors only, using mean values across all imputations); darker points indicate more patients with identical values. DAWOLS after 28 and 90 days are presented on the horizontal axes, while HRQoL values (EQ VAS or EQ-5D-5L index values) are presented on the vertical axes. The predicted values according to the best fitting fractional polynomial transformation models from both trials are presented with 95% confidence bands; predictions based on the best model from the HOT-ICU trial are presented in blue with full lines, while predictions based on the best model from the COVID STEROID 2 trial are presented in red with dashed lines (external validation). DAWOLS28/90, days alive without life support after 28 or 90 days; EQ-5D-5L, EuroQol 5-dimension 5-level survey; EQ VAS, EuroQol visual analogue scale; HRQoL, health-related quality of life.

from the sensitivity analyses using the Danish value set for EQ-5D-5L index values in all patients and the sensitivity analyses excluding patients with partially complete DAOOH after 28 days from the HOT-ICU trial were largely similar with the primary results.

4 | DISCUSSION

In this study of associations between DAWOLS or DAOOH and HRQoL in severely or critically ill adults included in the COVID STEROID 2 and HOT-ICU trials, we found weak or poor associations in the primary analyses conducted in survivors at HRQoL-follow-up only. We observed substantial scatter and relatively high RMSEs of the best model fits, both in the trial datasets, where models were fitted, and when assessed in the alternate trial datasets, where poor calibration was observed for all models. For the individual EQ-5D-5L domains, we found that patients in worse categories generally had fewer DAWOLS or DAOOH at both 28 and 90 days. Finally, in sensitivity analyses including non-survivors assigned 0 for HRQoL and either 0 or the actual values for DAWOLS/DAOOH, we found moderate associations (increasing HRQoL with the increase in DAWOLS or DAOOH), although RMSEs and external calibration were still relatively poor. Taken together, associations between DAWOLS or DAOOH at day 28 or 90 and HRQoL assessed using EQ-5D-5L index values or EQ VAS were generally weak and uncertain, except when including non-survivors. Predictions of HRQoL based on DAWOLS or DAOOH are, therefore, too uncertain to be meaningful.

The poor associations between DAWOLS or DAOOH and HRQoL may be explained by multiple factors. First, as HRQoL is generally measured much later than DAWOLS or DAOOH,[2] it may be affected by many external factors and events happening after ICU or hospital discharge.[34] Second, EQ-5D-5L domains and especially EQ VAS scores may be hypothesised to be somewhat volatile and expected to vary from day to day making the detection of associations more difficult due to the high variation. Third, long-term HRQoL in survivors of critical illness may be substantially affected by HRQoL prior to hospitalisation with the hospital admission contributing less to overall HRQoL as time from discharge increases.[35] The lack of convincingly strong associations between DAWOLS or DAOOH and HRQoL precludes using DAWOLS or DAOOH to predict HRQoL, and these shorter-term outcomes can, thus, not be considered reliable proxies of long-term HRQoL. Importantly, the lack of strong associations does not invalidate the use of either type of outcome; rather, it may serve as an argument to collect both outcomes in RCTs where they are of clinical interest. Both outcome types come with important advantages and disadvantages, and both may be considered important to patients.[3,4,14,36,37] Ultimately, the choice of outcomes in critical care trials should depend on multiple considerations, including

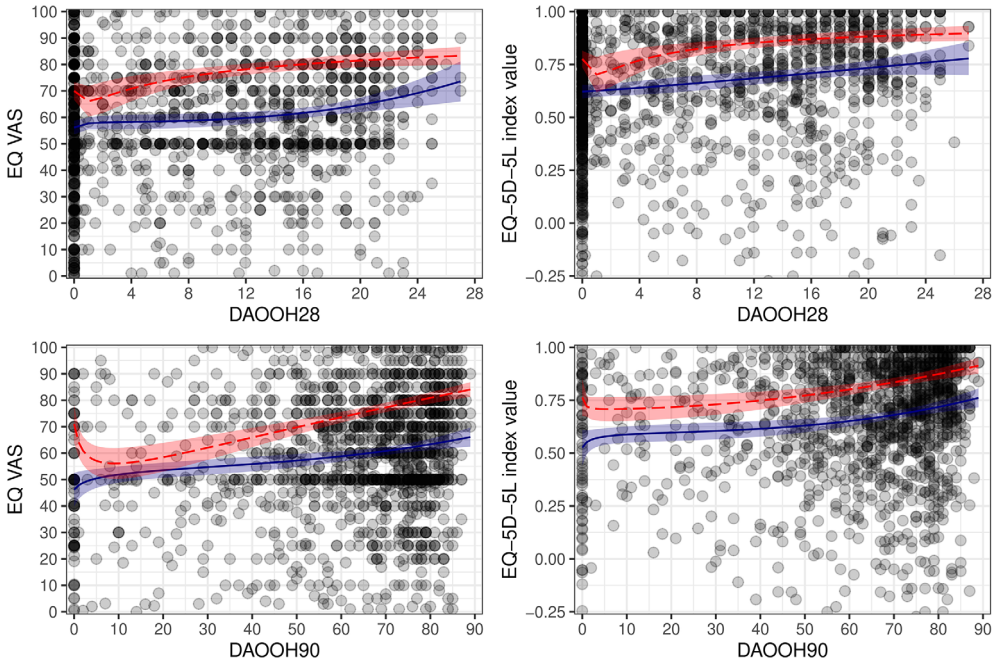

FIGURE 4 Associations between DAOOH and HRQoL in survivors only the HOT-ICU trial. Scatter plots with data from the HOT-ICU trial using the multiply imputed datasets (survivors only, using mean values across all imputations); darker points indicate more patients with identical values. DAOOH after 28 and 90 days are presented on the horizontal axes, while HRQoL values (EQ VAS or EQ-5D-5L index values) are presented on the vertical axes. The predicted values according to the best fitting fractional polynomial transformation models from both trials are presented with 95% confidence bands; predictions based on the best model from the HOT-ICU trial are presented in blue with full lines, while predictions based on the best model from the COVID STEROID 2 trial are presented in red with dashed lines (external validation). DAOOH28/90, days alive out of hospital after 28 or 90 days; EQ-5D-5L, EuroQol 5-dimension 5-level survey; EQ VAS, EuroQol visual analogue scale; HRQoL, health-related quality of life.

relevance to patients, assessment time-frames, methodological concerns (including the handling of non-survivors and missing data[3]) and expectations about which outcomes may be reasonably affected by the interventions assessed.

4.1 | Strengths and limitations

This study comes with several strengths. These include the pre-specification and publication of the protocol[11] before HRQoL-follow-up was completed for the COVID STEROID 2 trial; the pre-defined sensitivity analyses including non-survivors using two different strategies and using the Danish value set in all patients;[11] the assessment of DAWOL and DAOOH at two different but commonly used time points; and finally, the assessment of associations and external validation of predictions in two different yet comparable RCT populations, which increases external validity.

The study has limitations, too. First, as expected,[11] the amounts of missing data were non-negligible in both trial databases for HRQoL. This was handled using multiple imputations as specified in the protocol,[11] since missingness for HRQoL data is unlikely to be missing-completely-at-random.[38] We assumed that missing data were missing-at-random and that missing data could be reasonably predicted from the other available data;[11] inherently, the missing-at-random assumption cannot be verified. Importantly, even if the data are not truly missing-at-random, multiple imputation is still expected to decrease bias and loss of power compared to (and so preferred over) complete case analyses, which were not conducted.[11,39] In addition to the expected missing data for HRQoL, data were only partially complete for DAOOH at Day 28 for 13.8% in the HOT-ICU trial. Importantly, the results were similar in our primary and post hoc sensitivity analyses with different handling of partially complete data for this outcome. Second, we did not assess whether associations differed in the two intervention arms in each trial; this was not planned as we did not expect this to be the case and as we found similar HRQoL data for survivors in both intervention groups in both trials.[17,18] Third, the assessment of HRQoL at two different time points in the two trials is a limitation that may partially explain the systematic over-/under-prediction observed when assessed externally in the other dataset, although we consider the external validation valuable and the systematic over-/under-prediction to be more likely to be explained by population differences. Fourth, although country-specific EQ-5D-5L value sets were available for most included patients, this was not the case for all countries, and we had to use the Danish value set for some non-Danish patients.[11,40] Importantly, the results were similar when comparing the primary analyses using different value sets and the sensitivity analysis using the Danish value set for all patients. Finally, DAWOLS or DAOOH may be more strongly

TABLE 1 Performance measures for the selected models for the primary analyses.

Days alive without…outcome	Spearman's rank correlation coefficient (95% CI)	RMSE (internal)	RMSE (external)	Calibration-in-the-large (external)	Calibration slope (external)
COVID STEROID 2: EQ VAS					
DAWOLS after 28 days	0.27 (0.19–0.34)	21.4	27.8	−16.9	−0.81
DAWOLS after 90 days	0.27 (0.19–0.34)	21.2	27.9	−17.1	0.43
DAOOH after 28 days	0.24 (0.16–0.31)	21.4	26.7	−15.8	1.22
DAOOH after 90 days	0.27 (0.19–0.34)	21.1	26.8	−16.1	1.08
COVID STEROID 2: EQ-5D-5L index values					
DAWOLS after 28 days	0.27 (0.20–0.35)	0.25	0.29	−0.16	4.07
DAWOLS after 90 days	0.28 (0.20–0.35)	0.25	0.30	−0.16	0.53
DAOOH after 28 days	0.24 (0.17–0.32)	0.25	0.29	−0.15	1.00
DAOOH after 90 days	0.27 (0.19–0.34)	0.24	0.29	−0.16	0.86
HOT-ICU: EQ VAS					
DAWOLS after 28 days	0.01 (−0.05 to 0.06)	26.3	30.2	13.9	0.10
DAWOLS after 90 days	0.02 (−0.04 to 0.07)	26.1	30.9	15.1	0.00
DAOOH after 28 days	0.12 (0.06–0.18)	26.1	30.5	15.5	0.57
DAOOH after 90 days	0.15 (0.09–0.20)	26.0	30.5	15.5	0.54
HOT-ICU: EQ-5D-5L index values					
DAWOLS after 28 days	0.04 (−0.02 to 0.09)	0.33	0.36	0.14	0.26
DAWOLS after 90 days	0.05 (0.00–0.10)	0.33	0.37	0.15	0.24
DAOOH after 28 days	0.15 (0.09–0.21)	0.33	0.37	0.15	0.87
DAOOH after 90 days	0.17 (0.11–0.22)	0.33	0.36	0.15	0.93

Note: Performance measures of the selected (the best-fitting) model for each association in each dataset for the primary analyses. Spearman's rank correlation coefficient is a non-parametric measure of the relationship between two variables ranging from −1 (one variable perfectly monotonically decreases as the other increases) through 0 (no monotonic relationship) to 1 (one variable perfectly monotonically increases as the other increases). RMSEs is a measure of the differences between values predicted by a statistical model and the observed values on the same scale as the dependent variable (EQ VAS or EQ-5D-5L index values here); RMSEs of 0 indicate perfect predictions, while increasing RMSEs indicate increased lack of fit, that is, that the model is increasingly worse at predicting the dependent variable (EQ VAS or EQ-5D-5L index values here) using the independent variable(s) (DAWOLS or DAOOH after 28 or 90 days here). RMSEs were assessed both in the trial dataset in which models were developed (internally) and in the other trial dataset (externally). The calibration-in-the-large was used to assess the model fit in the other trial dataset (externally) and corresponds to the mean prediction error; ideally, this value is 0, while values >0 and <0 indicate systematic over- and under-prediction, respectively, of the dependent variable (EQ VAS or EQ-5D-5L-index values here).[31] Calibration slopes were similarly used to assess the model fit in the other trial dataset (externally) and measures systematic over- or underfitting of models, with values of 1 being ideal, while values <1 and >1 suggest too extreme or too moderate predictions, respectively.[31]
Abbreviations: CI, confidence interval; DAOOH, days alive out of hospital; DAWOLS, days alive without life support; EQ-5D-5L, EuroQol 5-dimension 5-level survey; EQ VAS, EuroQol Visual Analogue Scale; RMSE, root mean squared error.

associated with changes from baseline (i.e., before severe or critical illness) in HRQoL than with absolute long-term HRQoL values. However, baseline HRQoL data are generally not registered in trials conducted in severely or acutely ill adults, including the COVID STEROID 2 and HOT-ICU trials, and consequently, we were unable to assess such associations in this study.

5 | CONCLUSIONS

We found limited or weak associations between DAWOLS or DAOOH and HRQoL in adult severely or critically ill patients included in the COVID STEROID 2 and HOT-ICU trials. There was substantial variability in outcomes, and prediction accuracy from the best fitted flexible models was poor both internally and externally in the alternate trial dataset, which also showed inadequate calibration. Although moderately strong associations were found when including non-survivors, this seemed mostly driven by the assignment of the value 0 for HRQoL in these patients.

AUTHOR CONTRIBUTIONS

Conception: Anders Granholm and Morten Hylander Møller. Study design: Anders Granholm, Olav Lilleholt Schjørring, Aksel Karl Georg Jensen, Bodil Steen Rasmussen and Morten Hylander Møller. Analysis: Anders Granholm and Thomas Lass Klitgaard. Drafting manuscript: Anders Granholm. Revision for critically important intellectual content and approval of the final version: all authors. Anders Granholm, Olav Lilleholt Schjørring, Aksel Karl Georg Jensen, Marie Warrer Munch, Thomas Lass Klitgaard, Elena Crescioli, Maj-Brit Nørregaard Kjær, Thomas Strøm, Theis Lange, Anders Perner, Bodil Steen Rasmussen

and Morten Hylander Møller were involved in the conduct or analysis of the COVID STEROID 2 trial and/or the HOT-ICU trial.

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DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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