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Health-related quality of life in survivors of septic shock: 6-month follow-up from the ADRENAL trial

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Abstract

Purpose: To investigate the impact of hydrocortisone treatment and illness severity on health-related quality of life (HRQoL) at 6 months in septic shock survivors from the ADRENAL trial.

Methods: Using the EuroQol questionnaire (EQ-5D-5L) at 6 months after randomization we assessed HRQoL in patient subgroups defined by hydrocortisone or placebo treatment, gender, illness severity (APACHE II < or ≥ 25), and severity of shock (baseline peak catecholamine doses < or ≥ 15 mcg/min). Additionally, in subgroups defined by post-randomisation variables; time to shock reversal (days), treatment with renal replacement therapy (RRT), and presence of bacteremia.

Results: At 6 months, there were 2521 survivors. Of these 2151 patients (85.3%-1080 hydrocortisone and 1071 placebo) completed 6-month follow-up. Overall, at 6 months the mean EQ-5D-5L visual analogue scale (VAS) was 70.8, mean utility score 59.4. Between 15% and 30% of patients reported moderate to severe problems in any given HRQoL domain. There were no differences in any EQ-5D-5L domain in patients who received hydrocortisone vs. placebo, nor in the mean VAS ($p = 0.6161$), or mean utility score ($p = 0.7611$). In all patients combined, males experienced lower pain levels compared to females [$p = 0.0002$). Neither higher severity of illness or shock impacted reported HRQoL. In post-randomisation subgroups, longer time to shock reversal was associated with increased problems with mobility ($p = < 0.0001$]; self-care ($p = 0.0.0142$), usual activities ($p = <0.0001$] and pain ($p = 0.0384$). Amongst those treated with RRT, more patients reported increased problems with mobility ($p = 0.0307$) and usual activities ($p = 0.0048$) compared to those not treated. Bacteraemia was not associated with worse HRQoL in any domains of the EQ-5D-5L.

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Conclusions: Approximately one fifth of septic shock survivors report moderate to extreme problems in HRQoL domains at 6 months. Hydrocortisone treatment for septic shock was not associated with improved HRQoL at 6 months. Female gender was associated with worse pain at 6 months.

Keywords: Health-related quality of life, Intensive care, Steroids, EQ5D, Sepsis, Septic shock

Introduction

Sepsis and septic shock are major global health problems, affecting at least 49 million people each year, with nearly eleven million dying [1–4]. Survivors of critical illness, including sepsis, often report reductions in quality of life (QoL) that are comprised of cognitive, physical and psychological problems which may last for months and years after discharge from intensive care [5–9]. Risk factors for the development of reduced QoL include greater severity of illness, prolonged mechanical ventilation, and increased duration of stay in the Intensive Care Unit (ICU) [6]. An association between increased shock severity and reduced QoL at 3 months has been reported in paediatric patients with septic shock, but this has not been investigated in adult patients [10].

In 2018, we reported the results of the adjunctive corticosteroid treatment in critically ill patients with septic shock (ADRENAL) trial which evaluated the effect of a continuous intravenous infusion of hydrocortisone vs. placebo on 90-day mortality in patients with septic shock [11]. Whilst no differences in 90-day or 6-month mortality were observed between the hydrocortisone and placebo groups [12], patients who received hydrocortisone had improved clinical outcomes such as faster shock resolution, shorter duration of mechanical ventilation, earlier time to ICU discharge and were less likely to require a blood transfusion. Whether hydrocortisone treatment of septic shock influence long-term QoL is unknown.

Health-Related Quality of Life (HRQoL) was a prespecified secondary outcome of the ADRENAL study [12–14]. We assessed HRQOL in survivors using the EuroQol, 5 Domain, 5 level (EQ-5D-5L) questionnaire at 6 months after randomization to investigate the impact of hydrocortisone treatment and severity of illness on long-term HRQoL in survivors of septic shock.

Take-home message

Approximately one fifth of septic shock survivors reports moderate to extreme problems in HRQoL domains. Hydrocortisone therapy for septic shock was not associated with improved HRQoL at 6 months.

Methods

Study design, participants and data source

Patients included in this study were those enrolled in the ADRENAL trial. The ADRENAL trial recruited 3800 patients between March 2013 and April 2017 from 69 ICUs across 5 countries. (Australia, New Zealand, Saudi Arabia, Denmark and the United Kingdom). The study was an investigator initiated, double blind, randomised controlled trial comparing 7 days of an intravenous infusions of hydrocortisone (200 mg/day) and a matching placebo in critically ill patients with septic shock requiring mechanical ventilation [13]. A detailed description of the study methods, and the results have been reported elsewhere [11, 13, 15].

Human research ethics committee approval was obtained for all participating sites before the study commenced enrolment of participants. Prior written consent or consent to continue was obtained from all participants or their legal representative, according to each jurisdiction's legal requirements.

At 6 months after randomisation, patients who had consented and were alive were contacted by blinded, trained research coordinators to conduct the HRQoL assessment using the EQ-5D-5L [14, 16]. which collates responses into five domains of HRQoL (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) with a five level score (no problems, slight problems, moderate problems, severe problems, extreme problems or unable). Quality of life utility values were calculated using the Australian algorithm with values generally ranging between 0 (death) to 1 (perfect health) [17]. Values below 0 are possible and represent health states considered worse than death. Respondents were also asked to rate their perceived health on a scale of 0 (worst) to 100 (best) called the visual analogue scale (VAS). Where patients were incapacitated due to their medical condition a proxy such as a caregiver, spouse, child, sibling or friend was interviewed. Numbers and proportion for the patient and proxy responses are reported. χ^2 test by interview method and HRQoL domains were conducted to test differences in reporting by interview method.

Available data collected included patients demographics, admission type, vital status, severity of illness (Acute Physiology And Chronic Health Evaluation (APACHE) II score) [18], use of mechanical ventilation, use of inotropes, time to randomisation, peak catecholamine dose

at randomisation, blood stream infections, time to shock reversal, use of renal replacement therapy (RRT) and EQ-5D-5L [14] at 6 months in those that survived.

We assessed HRQoL in all patients with septic shock by randomised treatment group (hydrocortisone vs. placebo). In addition, we investigated HRQoL in subgroups determined by pre-randomisation variables: high (≥ 25) vs. low (< 25) severity of illness (APACHE II) score [18], female vs. male gender, peak catecholamine dose at randomization of < or ≥ 15 mcg/min (severity of shock), and defined by post-randomisation variables; time to shock reversal (days), those treated or not with already abbreviated above RRT during the study, and in those with or without new/repeated bacteremia during the study.

For female vs. male, the definition for collection was to select the appropriate sex (male or female) which corresponded to the patient's legal gender. The legal gender was defined as the gender listed on the birth certificate. For the purpose of this study, we respectfully refer to sex and/or gender as 'gender'.

Statistical analysis

Baseline characteristics were compared between hydrocortisone and placebo within the cohort of survivors who had HRQoL data available. χ^2 test and t test were used for categorical and continuous variables, respectively.

All patients who were alive at 6 months and answered the EQ-5D-5L were included. Responses to the EQ-5D-5L are presented by 5 domains and 5 levels. Responses were also converted into HRQoL utility scores using the Australian published tariffs and were reported as a continuous outcome with means and Standard Deviations (SD). The VAS responses were also reported as continuous outcomes (Mean and SD).

Associations for the pre and post-randomisation variables and HRQoL outcomes were presented as odds ratios (OR) and 95% confidence intervals (CI) for binary outcomes (no problems vs. moderate to extreme problems) based on a logistic model and Mean Differences (MD) and 95% CI for continuous outcomes based on a linear model. Adjusted associations are presented in the results for significant variables. Variables for the adjusted model were selected from pre-specified covariates included in the main ADRENAL paper (including age, gender, APACHE II score, admission type, site of sepsis (pulmonary vs. other), randomization (hydrocortisone vs. placebo), and baseline therapy (mechanical ventilation, inotrope/vasopressor use). Significance level was set at p = 0.05. All tests were two-sided and the nominal level of α was 5%. SAS Enterprise Guide 7.1 was used for analyses.

Sensitivity analysis

Sensitivity analyses were conducted to determine if any differences existed between those that survived, were lost to follow-up or had missing HRQoL data. Baseline characteristics were compared with χ^2 test and t test used for categorical and continuous variables, respectively. In addition, imputation for patients who died at 6 months was conducted for HRQoL utility scores (imputing a zero value) for all reported clinical groups of interest.

Results

Between March 2013 and April 2017 a total of 2151/2521 (85.3%) ADRENAL participants who were alive completed follow-up at 6 months which included 1080/1265 participants in the hydrocortisone group and 1071/1256 participants in the placebo group (Fig. 1).

Participant baseline characteristics (prior to randomization) are reported in Table 1 between hydrocortisone and placebo groups. The characteristics of the two group were well matched with no significant differences noted.

Health-related quality of life

Participants completed the HRQoL questionnaire 75.8% (1630/2151) of the time and a proxy 24.2% (521/2151) of the time. The proxy was more likely to report moderate to extreme problems for mobility, self-care, and usual activity but not for pain, discomfort and anxiety/depression (eTables 10–11).

Overall, at 6 months after randomisation the mean VAS was 70.8, mean utility score 59.4, with between 15% and 30% of patients reporting moderate to severe problems in any given domain (Table 2).

For those patients receiving hydrocortisone compared with placebo, the mean VAS was 71.1 vs. 70.6 [adjusted MD 0.39; 95% CI −1.39 to 2.171), respectively. The mean utility score was 59.6 vs. 59.2 (adjusted MD 0.01; 95% CI −0.03 to 0.04), respectively (Tables 2, 3).

For gender, the odds of experiencing moderate to extreme pain was lower for males compared to females (adjusted OR 0.69; 95% CI 0.57 to 0.84]; $p = 0.0002$) (Fig. 2, Table 3, eTable 3).

In patient with high severity of illness and severity of shock, no differences between moderate to extreme problems were reported in any of the HRQoL domains nor in the VAS or utility score (Table 3, eTables 4 and 5).

In patients receiving RRT at any time during the study, the odds of experiencing moderate to extreme problems with mobility (adjusted OR 1.30; 95% CI 1.02

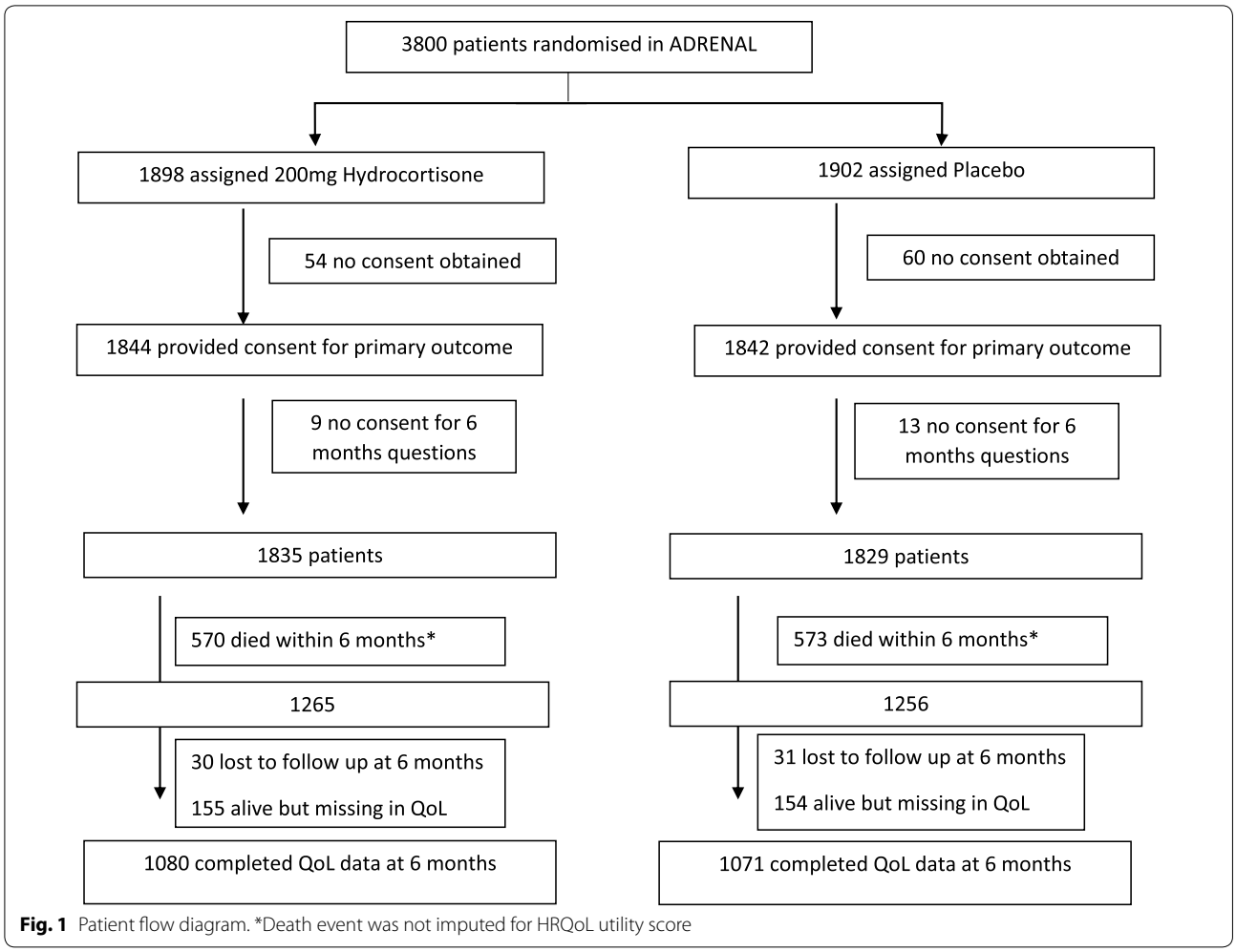

Fig. 1 Patient flow diagram. *Death event was not imputed for HRQoL utility score

to 1.65; $p = 0.0307$) and usual activities (adjusted OR 1.39; 95% CI 1.11 to 1.75; $p = 0.0048$) were higher compared with those that didn't receive RRT at any time during the study (Table 3, eTable 7).

A longer time to shock reversal (>7 days vs. <=2 days) was associated with an increase in the odds of patients reporting moderate to extreme problems in mobility (adjusted OR 2.11; 95% CI 1.51 to 2.96; $p = < 0.0001$), self-care (adjusted OR 1.76; 95% 1.17 to 2.65; $p = 0.0068$), and usual activities (adjusted OR 2.10; 95% CI 1.52 to 2.91; $p = < 0.0001$). Mean utility scores also reflected worse health states the longer time to shock reversal (adjusted MD −0.08; 95% CI −0.14 to -0.03]; $p = 0.0018$) (Table 3, eTable 6).

No differences in moderate to extreme problems with HRQoL were reported between patients with new bacteraemia compared with no bacteraemia in any of the 5 domains of EQ-5D-5L nor in the mean VAS or utility scores (Table 3, eTable 8).

Sensitivity analysis

Baseline characteristics between those that survived, were lost to follow up or had missing EQ-5D-5L, and those who died did not show significant differences (eTable 1). When the results were imputated for patients who died at 6 months the utility scores for RRT and severity of shock (peak catecholamine dose) were different as compared to the main results, where both showed significant associations with worse HRQoL (eTable 9).

Discussion

Key findings

We found that survivors of septic shock have low indices of reported quality of life and between 15 and 30% report moderate to extreme problems in the various domains of HRQoL. The administration of hydrocortisone did not result in an improved HRQoL. Females were more likely to experience moderate to extreme pain at 6 months compared to males.

Table 1 Baseline characteristics of survivors between hydrocortisone and placebo

Variable	Hydrocortisone (*N* = 1265)	Placebo (*N* = 1256)	*p* value
Gender			0.8258
Female	507/1265 (40.1%)	498/1256 (39.6%)	
Age (years)			
Mean (SD)	60.4 (14.95)	60.7 (15.45)	0.625
Weight (kgs)			
Mean (SD)	87.6 (27.92)	87.2 (26.59)	0.681
Country			0.9945
New Zealand	151/1265 (11.9%)	149/1256 (11.9%)	
Australia	930/1265 (73.5%)	920/1256 (73.2%)	
United Kingdom	106/1265 (8.4%)	108/1256 (8.6%)	
Denmark	39/1265 (3.1%)	42/1256 (3.3%)	
Saudi Arabia	39/1265 (3.1%)	37/1256 (2.9%)	
Admission type			0.8341
Non-operative	834/1262 (66.1%)	833/1253 (66.5%)	
Operative	428/1262 (33.9%)	420/1253 (33.5%)	
Apache II			
Mean (SD)	22.7 (7.29)	22.7 (7.61)	0.9487
Mechanical ventilated			0.1819
Yes	1258/1262 (99.7%)	1252/1253 (99.9%)	
Inotropes or vasopressors at the time of randomisation			0.4115
Yes	1257/1265 (99.4%)	1251/1256 (99.6%)	
Vasopressin			0.2379
Yes	184/1265 (14.5%)	204/1256 (16.2%)	
Antimicrobials in the 24 h prior to randomisation			0.3399
Yes	1243/1261 (98.6%)	1229/1253 (98.1%)	
RRT in the 24 h prior to randomisation			0.8456
Yes	116/1262 (9.2%)	118/1253 (9.4%)	
Highest arterial lactate mmol/L			
Mean (SD)	3.3 (2.64)	3.3 (2.58)	0.817
Highest creatinine umol/L			
Mean (SD)	183.9 (171.25)	178.8 (151.8)	0.4255
Median (Q1;Q3)	134 (85;217)	132 (85.5;212.0)	
Lowest PaO2/FIO2 ratio			
N	1247	1247	
Mean (SD)	170.4 (93.97)	169 (91.67)	0.6994
Median (Q1;Q3)	146 (98;228)	148 (96;220)	
First site of infection			0.4149
Pulmonary	470/1259 (37.3%)	516/1250 (41.3%)	
Abdominal	282/1259 (22.4%)	253/1250 (20.2%)	
Blood	208/1259 (16.5%)	201/1250 (16.1%)	
Skin or soft tissue	101/1259 (8%)	83/1250 (6.6%)	
Urinary	96/1259 (7.6%)	101/1250 (8.1%)	
Other	102/1259 (8.1%)	96/1250 (7.7%)	
Time from ICU admission to randomisation (h)			
Mean (SD)	26.2 (74.67)	27.4 (67.78)	0.6829
Median (Q1;Q3)	13.9 (8.2;22.2)	14.9 (8.3;23.7)	
Time from inotropes use to randomisation (hrs)			
Mean (SD)	20.1 (81.24)	20.2 (73.23)	0.9811
Median (Q1;Q3)	12.4 (7.2;19.3)	13 (7.1;19.6)	

Table 1 (continued)

Variable	Hydrocortisone (*N* = 1265)	Placebo (*N* = 1256)	*p* value
Catecholamine dose			0.3019
> 15 mcg/minute	540/1254 (43.1%)	507/1236 (41%)	
≤ 15 mcg/minute	714/1254 (56.9%)	729/1236 (59%)	
Site of sepsis			0.1002
Others	734/1265 (58.0%)	688/1256 (54.8%)	
Pulmonary	531/1265 (42.0%)	568/1256 (45.2%)	
APACHE II score			0.6053
< 25	775/1261 (61.5%)	782/1252 (62.5%)	
≥ 25	486/1261 (38.5%)	470/1252 (37.5%)	
Time of onset shock to randomisation			0.2722
< 6 h	239/1257 (19%)	237/1251 (18.9%)	
6 to < 12 h	367/1257 (29.2%)	330/1251 (26.4%)	
12 to < 18 h	303/1257 (24.1%)	296/1251 (23.7%)	
≥ 18 h	348/1257 (27.7%)	388/1251 (31%)	

Relationship to previous studies

Our findings of poor self-reported HRQoL at 6 months align with prior studies in sepsis and critical illness [6, 9, 19, 20]. In a recent report of HRQoL and 1-year survival in early septic shock, patients randomised to early goal directed therapy or usual care self-reported their HRQoL using the EQ-5D-3L with VAS scores of 66.0 and 66.3 between groups, respectively (population norms 81.6; this cohort 70.8).

In a secondary analysis of two international RCTs in patients with severe sepsis [9] long-term HRQoL was measured using the EQ-5D-3L at 6 months, which also reported similar decrements in health to our study, particularly in the functional domains of mobility, usual activities and self-care.

The findings in our study demonstrating differences between genders in self-reported HRQoL scores aligns with previous research in other patient populations [21]. Specifically, our results showed females were more likely to report moderate to extreme levels of pain at 6 months. These differences may be partly explained by comorbidities or other sociodemographic factors which we were unable to control for. Further research is being undertaken to understand if gender is a treatment effect modifier for hydrocortisone in this patient population.

Our study identified that the need for RRT and longer time to shock reversal were associated with reduced HRQoL for patients. Use of RRT has previously been shown to be associated with low quality of life [22]. Whilst steroids influence shock reversal and time to ICU discharge favorably, it did not translate to improved long-term HRQoL in our study. Steroids do have the propensity to cause myopathy, adversely affect neuromuscular function and delay recovery [23] suggesting a possible mechanism potentially countering any benefits seen during the acute phase of septic shock.

The association between reported pre and post-randomisation variables and 6-month HRQoL observed in our study differ from those that were reported by Yende and colleagues [9, 24]. They modelled predictors of impaired HRQoL in the domains for mobility and self-care at 6 months and found that duration of organ support (measured by ventilation and dialysis use for 1–14 days or more than 14 days, or vasopressor use for 1–7 days or 7 or more days) did not impact on either domain. The possible reasons for the differences between our studies could be related to differences in the patient definitions used for septic shock (ACCESS [24] included both severe sepsis and septic shock patients with septic shock defined as hypotension requiring vasopressors. ADRENAL [12] only included septic shock patients whom required vasopressors/inotropes for minimum of 4 h plus mechanical ventilation) [9, 11].

Strengths and limitations

This represents the largest study of HRQoL assessment in a cohort of patients with septic shock. The endpoint of this study was a pre-specified secondary outcome from the ADRENAL trial and all the data were collected in the context of a large, pragmatic, randomised control trial. [11] The follow-up was conducted by trained research coordinators who were blinded to the treatment allocation. Follow-up success rate exceeded 80% which is similar or higher than other similar studies [9, 19, 25]. The inclusion of 69 sites from 5 countries increases the generalizability of the results. The EQ-5D-5L is a valid, easily

Table 2 EuroQol-5D-5L at 6 months between hydrocortisone and placebo (unadjusted)

Variable	Hydrocortisone (*N* = 1080)	Placebo (*N* = 1071)	Total (*N* = 2151)	*p* value
Mobility				0.7720
I have no problems with walking around	564/1080 (52.2%)	548/1071 (51.2%)	1112/2151 (51.7%)	
I have slight problems with walking around	225/1080 (20.8%)	214/1071 (20.0%)	439/2151 (20.4%)	
I have moderate problems with walking around	153/1080 (14.2%)	170/1071 (15.9%)	323/2151 (15.0%)	
I have severe problems with walking around	67/1080 (6.2%)	73/1071 (6.8%)	140/2151 (6.5%)	
I am unable to walk around	71/1080 (6.6%)	66/1071 (6.2%)	137/2151 (6.4%)	
Self-care				0.0972
I have no problems with washing or dressing myself	765/1080 (70.8%)	772/1071 (72.1%)	1537/2151 (71.5%)	
I have slight problems with washing or dressing myself	166/1080 (15.4%)	126/1071 (11.8%)	292/2151 (13.6%)	
I have moderate problems with washing or dressing myself	76/1080 (7.0%)	88/1071 (8.2%)	164/2151 (7.6%)	
I have severe problems with washing or dressing myself	31/1080 (2.9%)	31/1071 (2.9%)	62/2151 (2.9%)	
I am unable to wash or dress myself	42/1080 (3.9%)	54/1071 (5.0%)	96/2151 (4.5%)	
Usual Activities				0.1345
I have no problems doing my usual activities	468/1080 (43.3%)	483/1071 (45.1%)	951/2151 (44.2%)	
I have slight problems doing my usual activities	287/1080 (26.6%)	236/1071 (22.0%)	523/2151 (24.3%)	
I have moderate problems doing my usual activities	159/1080 (14.7%)	181/1071 (16.9%)	340/2151 (15.8%)	
I have severe problems doing my usual activities	81/1080 (7.5%)	89/1071 (8.3%)	170/2151 (7.9%)	
I am unable to do my usual activities	85/1080 (7.9%)	82/1071 (7.7%)	167/2151 (7.8%)	
Pain Discomfort				0.8190
I have no pain or discomfort	494/1080 (45.7%)	480/1071 (44.8%)	974/2151 (45.3%)	
I have slight pain or discomfort	296/1080 (27.4%)	301/1071 (28.1%)	597/2151 (27.8%)	
I have moderate pain or discomfort	191/1080 (17.7%)	202/1071 (18.9%)	393/2151 (18.3%)	
I have severe pain or discomfort	75/1080 (6.9%)	70/1071 (6.5%)	145/2151 (6.7%)	
I have extreme pain or discomfort	24/1080 (2.2%)	18/1071 (1.7%)	42/2151 (2.0%)	
Anxiety Depression				0.7841
I am not anxious or depressed	627/1080 (58.1%)	608/1071 (56.8%)	1235/2151 (57.4%)	
I am slightly anxious or depressed	225/1080 (20.8%)	235/1071 (21.9%)	460/2151 (21.4%)	
I am moderately anxious or depressed	161/1080 (14.9%)	151/1071 (14.1%)	312/2151 (14.5%)	
I am severely anxious or depressed	52/1080 (4.8%)	57/1071 (5.3%)	109/2151 (5.1%)	
I am extremely anxious or depressed	15/1080 (1.4%)	20/1071 (1.9%)	35/2151 (1.6%)	
QoL AUS utility score				0.7611
n	1080	1071	2151	
Mean (SD)	0.59 (0.3416)	0.592 (0.3453)	0.594 (0.3434)	
QoL VAS score				0.6161
N Mean (SD)	1068 71.1 (20.76)	1057 70.6 (21.01)	2125 70.8 (20.88)	

administered, quality of life assessment tool that is available in more than 130 languages and has been used in a number of high quality randomised trials in intensive care patients, including in patients with sepsis [9, 19, 25, 26]. The use of the 5 level version also allowed for better responsiveness of patients self-reported HRQoL with 75% of responses completed by the participant in our study.

Within the context of a large pragmatic trial, we did not collect data on concurrent illnesses and post care after the index hospital discharge and before the 6-month follow-up which may have confounded the HRQoL assessment [27]. The EQ-5D-5L questionnaire has some limitations including that it is a preference based measure that is mainly used to determine Quality Adjusted Life Year scores for cost effective analysis. However, the EQ-5D-5L has been tested for responsiveness (the ability to detect health status change) and is considered to be able to do so effectively [28]. We did not account for patients who died as the primary aim was to evaluate HRQoL in survivors at 6 months, but we performed a sensitivity analysis to determine any differences in those that died or had missing HRQoL data.

Table 3 Multivariate model of HRQoL

Variable	Mobility OR (95% CI)	Self-care OR (95% CI)	Usual activities OR (95% CI)	Pain OR (95% CI)	Anxiety/ Depression OR (95% CI)	VAS MD (95% CI)	Utility MD (95% CI)
Treatment	$p=0.3145$	$p=0.1167$	$p=0.1772$	$p=0.9019$	$p=0.9881$	$p=0.6676$	$p=0.8128$
Placebo	1	1	1	1	1	0	0
Hydrocortisone	0.90 (0.75 to 1.097)	0.826 (0.65 to 1.049)	0.881 (0.734 to 1.059)	0.988 (0.815 to 1.197)	1.002 (0.812 to 1.235)	0.39 (− 1.39 to 2.171)	0.004 (− .026 to 0.033)
Gender	$p=0.8987$	$p=0.8371$	$p=0.0508$	$p=0.0002$	$p=0.0939$	$p=0.9896$	$p=0.2632$
Female	1	1	1	1	1	0	0
Male	0.99 (0.81 to 1.20)	1.03 (0.80 to 1.31)	0.83 (0.69 to 1)	0.69 (0.57 to 0.84)	0.83 (0.67 to 1.03)	− 0.01 (− 1.84 to 1.81)	0.02 (− 0.01 to 0.05)
APACHE	$p=0.0679$	$p=0.3285$	$p=0.3106$	$p=0.616$	$p=0.4508$	$p=0.0807$	$p=0.1607$
< 25	1	1	1	1	1	0	0
25 or more	1.35 (0.98 to 1.85)	1.22 (0.82 to 1.82)	1.17 (0.86 to 1.6)	1.09 (0.79 to 1.5)	1.15 (0.8 to 1.64)	− 2.67 (− 5.68 to 0.33)	− 0.04 (− 0.08 to 0.01)
Baseline peak catecholamine dose	$p=0.4564$	$p=0.9944$	$p=0.6274$	$p=0.3803$	$p=0.4271$	$p=0.9751$	$p=0.727$
≤ 15	1	1	1	1	1	0	0
> 15	1.08 (0.88 to 1.32)	1 (0.78 to 1.29)	1.05 (0.86 to 1.27)	0.91 (0.74 to 1.12)	0.91 (0.73 to 1.14)	0.03 (− 1.87 to 1.93)	0.01 (− 0.03 to 0.04)
RRT received during FU	$p=0.0307$	$p=0.7115$	$p=0.0048$	$p=0.1517$	$p=0.8049$	$p=0.305$	$p=0.1455$
No	1	1	1	1	1	0	0
Yes	1.30 (1.02 to 1.65)	0.94 (0.7 to 1.28)	1.39 (1.11 to 1.75)	1.19 (0.94 to 1.52)	0.97 (0.74 to 1.27)	− 1.19 (− 3.46 to 1.08)	− 0.03 (− 0.06 to 0.01)
Time to shock resolution	$p=<.0001$	$p=0.0142$	$p=<.0001$	$p=0.0384$	$p=0.6954$	$p=0.1915$	$p=0.0006$
≤ 2 days	1	1	1	1	1	0	0
3–4 days	1.44 (1.15 to 1.8)	1.25 (0.94 to 1.66)	1.3 (1.05 to 1.61)	1.36 (1.09 to 1.7)	1.04 (0.82 to 1.32)	− 1.55 (− 3.61 to 0.52)	− 0.06 (− 0.09 to − 0.02)
5–7 days	1.9 (1.41 to 2.55)	1.62 (1.12 to 2.33)	1.44 (1.08 to 1.93)	1.13 (0.83 to 1.54)	0.85 (0.6 to 1.2)	− 1.74 (− 4.57 to 1.09)	− 0.06 (− 0.11 to − 0.02)
> 7 days	2.11 (1.51 to 2.96)	1.76 (1.17 to 2.65)	2.1 (1.52 to 2.91)	1.39 (0.99 to 1.97)	1.06 (0.73 to 1.56)	− 3.21 (− 6.48 to 0.07)	− 0.08 (− 0.14 to − 0.03)
Bacteremia during FU	$p=0.3168$	$p=0.5233$	$p=0.1906$	$p=0.0864$	$p=0.8521$	$p=0.9463$	$p=0.5074$
No	1	1	1	1	1	0	0
Yes	1.14 (0.88 to 1.49)	1.11 (0.8 to 1.55)	1.19 (0.92 to 1.53)	1.26 (0.97 to 1.64)	1.03 (0.77 to 1.38)	0.09 (− 2.45 to 2.62)	− 0.01 (− 0.06 to 0.03)

p value shown for shock reversal is the *p* value for the trend using ordered category of shock reversal. *p* value for > 7 days vs. ≤ 2 days provided in text

Pre-specified baseline covariates for adjustment, plus randomisation allocation *adjusted model: adjusted for baseline age, sex, APACHE II score, admission type (operative vs. non-operative), site of sepsis pulmonary vs. other, baseline therapy use including vasopressin, adrenaline and other type, plus randomisation (hydrocortisone vs. placebo)

Clinical implications and future direction

Our study provides new hypothesis generating information about the potential importance of delay in reversal of shock in the acute phase of the illness and the resultant impact on long-term HRQoL. Whilst macro and micro circulatory abnormalities in septic shock have been reported to be associated with long-term mortality [29, 30], this is the first report to describe the impact of delayed shock reversal in the acute phase on long-term quality of life in adult patients with septic shock. Whilst the precise mechanism of the basis of this finding was not investigated in this study, persistent shock is associated with cellular and metabolic abnormalities, and organ dysfunction [31], particularly involving the central nervous and musculoskeletal systems which are key elements in the HRQoL assessment. In the original ADRENAL trial, we had reported improvement in secondary

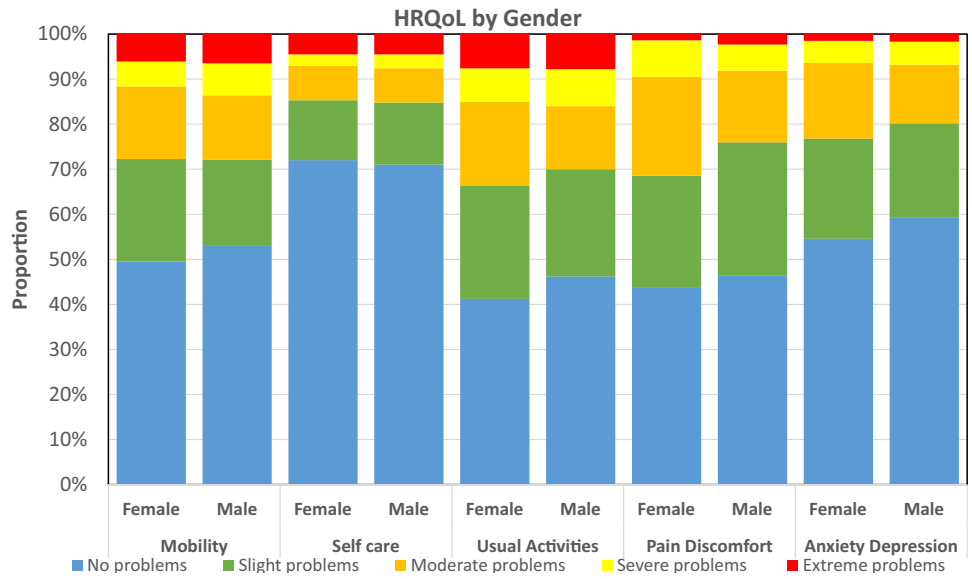

Fig. 2 EuroQol-5D-5L at 6 months for gender

outcomes in the hydrocortisone group (earlier reversal of shock, earlier liberation from mechanical ventilation, and faster time to discharge from ICU). The lack of a difference between the hydrocortisone and placebo groups in HRQoL, despite earlier shock reversal in the former, may be due to the lack of statistical power.

Studies of associations, especially ones including post-randomisation variables are subject to confounding, as such, the association between the post-randomisation groups and HRQoL outcomes at 6 months were hypothesis generating with model estimates interpreted with caution and will need to be investigated further in future randomised controlled trials.

Conclusions

In conclusion, approximately one fifth of septic shock survivors report moderate to extreme problems in HRQoL domains at 6 months. Hydrocortisone treatment for septic shock was not associated with improved self-reported HRQoL at 6 months. Female patients reported worse pain in the EQ-5D-5L at 6 months.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-020-06169-1) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest
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