Assessing the impact of physical, mental and cognitive impairments on health-related quality of life in sepsis survivors following intensive care admission in New Zealand

Patrice Rosengrave, Jonathan Williman, Geoff Shaw, Anitra C Carr

ABSTRACT

AIM: To assess the impact of physical, mental and cognitive impairments on health-related quality of life (QoL) of individuals who have survived sepsis after admission to an intensive care unit (ICU) in New Zealand.

METHODS: Survivors from a trial investigating vitamin C as an adjunctive therapy in patients with sepsis in Christchurch Hospital ICU were invited to enrol in a longitudinal QoL follow-up study. Patients were interviewed at hospital discharge, 30, 90 and 180 days, using validated physical and mental health assessment questionnaires (Short-Form-36, EuroQol-5-Dimension). Cognitive function was monitored and results compared with New Zealand population norms.

RESULTS: Eighteen of the 26 survivors participated in the 6-month QoL follow-up. At hospital discharge, there were significant physical and mental health issues in the participants interviewed, and although a majority of the subscales improved over the 6-month follow-up, physical function, role—physical and general health were still below population norms. Following discharge, objective parameters (mobility, self-care, usual activities) normalised within 3–6 months, while subjective measures (pain/discomfort and anxiety/depression) improved earlier and were better than population norms at 3–6 months. Cognitive dysfunction persisted over the follow-up period. Short-term (4-day) vitamin C intervention in the ICU did not affect health parameters post–hospital discharge.

CONCLUSIONS: Survivors of septic shock experience elevated physical, mental and cognitive issues at discharge. Most mental health issues had resolved by 6 months, but some physical and cognitive issues had not returned to population norms. Short-term vitamin C administration did not improve long-term health-related QoL; however, ongoing vitamin C supplementation may be required.

Septic shock is a life-threatening response to severe infection characterised by profound circulatory, cellular and metabolic abnormalities.[1] Septic shock has mortality rates greater than 40%, with comorbidities and older age being major contributors.[1] The incidence of sepsis is continuing to grow globally, driven by an ageing population.[2,3] Septic shock is managed through empiric antimicrobial therapy, source control of infection, fluid resuscitation, vasopressor administration and organ support via mechanical ventilation and renal replacement therapy.[4] As a result of both the disease process and invasive interventions in the intensive care unit (ICU), patients who survive sepsis can experience long-term physical disabilities, cognitive dysfunction and psychological issues such as anxiety and depression, which significantly affect their health-related quality of life (QoL) and ability to live independently.[5] There are currently limited longitudinal data within the first 6 months of hospital discharge, with QoL questionnaires primarily being administered from 6 months onwards.[6–11] Furthermore, there are limited data from a New Zealand context, with many trials comprising mixed cohorts.[6,8,9] To address these gaps in the literature, comprehensive post-discharge QoL data comprising physical, mental and cognitive function measures were collected from a small New Zealand ICU cohort during the first 6 months following hospital discharge and compared with New Zealand population norms.

The QoL follow-up cohort comprised a sub-group from a randomised controlled trial (RCT) investigating the effects of vitamin C as an adjunctive therapy in patients with septic shock.[12] Vitamin C is an essential nutrient with numerous supportive functions in the immune, respiratory, cardiovascular and central nervous systems.[13–15] Critically ill patients with sepsis have severely

depleted circulating concentrations of the vitamin, lower than non-septic patients and only one-third the concentration of the general population,[16] despite recommended enteral and parenteral intakes, suggesting a higher turnover and requirement for the vitamin in these patients.[17] In fact, requirements appear to be at least 10-fold higher than non-hospitalised individuals, with parenteral administration of up to 2–3 grams required to saturate the blood.[18,19] Furthermore, due to vitamin C's water-soluble nature, it is not retained by the body and is lost through urine;[20] therefore, there is an ongoing need for supplementation after hospital discharge.[14]

To our knowledge, no comprehensive studies have assessed the effects of vitamin C intervention on the post-discharge QoL outcomes of survivors of septic shock. Vitamin C administration to critically ill patients with sepsis may improve organ function, as evidenced in various trials by reduced requirements for fluid resuscitation, vasopressor administration, mechanical ventilation and renal replacement therapy,[14,21] which could be anticipated to improve long-term patient QoL. Vitamin C also has numerous important functions in the central nervous system, with neurological tissue containing some of the highest concentrations of vitamin C in the body.[15] Furthermore, observational and interventional studies have shown inverse associations between vitamin C and cognitive dysfunction, as well as mental health disorders such as depression and anxiety.[22,23] Thus, we hypothesised that administering vitamin C to patients with septic shock may improve measures of post-discharge health-related QoL.

Methods

Participant enrolment and intervention

The current study comprised a 6-month QoL follow-up of septic shock participants enrolled in an intravenous (IV) vitamin C RCT in Christchurch Hospital, described previously.[12] Ethical approval for the main trial and the follow-up study was obtained from the New Zealand Northern A Health and Disability Ethics Committee (16NTA238). The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617001184369). Participants meeting the study inclusion criteria for septic shock were randomised (1:1) to receive either placebo infusions or up to 96 hours of IV vitamin C (total dose of 100mg/kg/day, administered 6 hourly), as described previously.[12] The clinical study coordinator, treating physicians and participants were blinded regarding treatment arm.

Collection of clinical and QoL data

Baseline data were collected between May 2018 and Dec 2019, and QoL follow-up data were collected between June 2018 and August 2020. Clinical data were collected and managed using Research Electronic Data Capture (REDCap), a secure, web-based data collection and storage tool hosted at the University of Otago, New Zealand. Data were de-identified using a patient study code. The following demographic and clinical data were recorded at baseline for the QoL study: age, gender, weight, ethnicity, primary diagnosis contributing to sepsis, comorbidities, ICU mortality and organ function performance scores (simplified acute physiology score [SAPS], acute physiology and chronic health evaluation [APACHE III] and sequential organ failure assessment [SOFA]), and ICU and hospital length of stay (LOS). QoL follow-up data were collected face-to-face at hospital discharge and then via phone call at days 30, 90 and 180 after discharge. Data for half of the patients were captured at hospital discharge, of which only two were in the vitamin C intervention arm.

Physical and mental health assessment (SF-36)

The Short Form-36 (SF-36, version 2) comprises 36 items to measure eight multi-item QoL domains: physical functioning (PF), role limitation due to physical problems (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitation due to emotional problems (RE) and mental health (MH).[24] It has demonstrated acceptability, reliability and validity in the ICU[25,26] and has New Zealand norms available.[27] The SF-36 also has two population-normalised summary scores, the Physical Component Summary (PCS) that comprises PF, RP, BP and GH, and the Mental Component Summary (MCS) that comprises VT, SF, RE and MH.[28] These values can be transformed to T-scores and thereby related to a population mean of 50 with each 10-point increment equivalent to a SD from the mean.[28]

Quality of life assessment (EQ-5D-5L)

The EuroQol 5 Dimension 5 Level (EQ-5D-5L) comprises a visual analogue scale (VAS) and five descriptive multi-item dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression issues.[29] The VAS records the

respondent's self-rated health on an analogue scale with the end points labelled "the best health you can imagine" and "the worst health you can imagine". Each descriptive dimension has five levels: no problems, slight problems, moderate problems, severe problems and extreme problems. These were converted into a single index value using an online calculator[30] and were based on New Zealand population valuation surveys that used VAS methods.[31]

Cognitive function assessment (COBRA)

Cognitive dysfunction was assessed using a 16-item self-reported Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA) questionnaire that measures subjective cognitive dysfunctions of executive function, processing speed, working memory, verbal learning and

Table 1: Participant baseline characteristics.

Parameter	Enrolled cohort (n=40)	Survivors (n=26)	QoL sub-group (n=18)
Age (y)	68 (61, 75)	65 (57, 71)	65 (60, 71)
Sex (male)	27 (67)	17 (65)	11 (61)
Ethnicity:			
NZ European	34 (85)	21 (81)	16 (89)
Māori	4 (10)	3 (12)	2 (11)
Pacific peoples	1 (3)	1 (4)	0 (0)
Other	2 (5)	1 (4)	0 (0)
Weight (kg)	80 (69, 98)	85 (72, 101)	94 (76, 107)
Sepsis source:			
Abdominal	14 (35)	11 (42)	9 (50)
Pulmonary	9 (23)	3 (12)	2 (9)
Skin/soft tissue	7 (18)	6 (23)	4 (22)
Blood	7 (18)	3 (12)	3 (16)
Other/unknown	6 (16)	4 (15)	1 (6)
SAPS2	50 (41, 58)	46 (39, 56)	49 (38, 58)
APACHE-III	84 (73, 97)	77 (68, 93)	85 (73, 95)
SOFA score	9.0 (7.0, 10)	9.0 (6.8, 10)	9.0 (6.8, 10)
ICU LOS	5.2 (2.7, 9.4)	4.5 (2.5, 9.8)	3.9 (2.4, 8.4)
Hospital LOS	13 (8, 31)	16 (9, 35)	14 (9, 29)
Number with comorbidities	9 (23)	7 (27)	5 (28)

Data represent n (%) or median (Q1, Q3).
APACHE = acute physiology and chronic health evaluation; ICU = intensive care unit; LOS = length of stay; QoL = quality of life; SOFA = sequential organ failure assessment; SAPS = simplified acute physiology score.

memory, attention/concentration and mental tracking.[32] All of the questions are rated using a 4-point scale: 0 = never, 1 = sometimes, 2 = often and 3 = always. The total score is obtained when the scores of each question are combined. Higher scores indicate the patient was experiencing more subjective complaints, the maximum score being 48 points.

Statistical analyses

Participant characteristics were summarised using descriptive statistics with continuous variables presented as mean or median and 95% confidence intervals (95% CI) or mean and standard deviation (SD), as indicated, and categorical variables as number and percentage. Correlations were carried out using Spearman's coefficient, with $p<0.05$ indicating statistical significance. Time course data were analysed using repeated measures mixed effects models (with Geisser–Greenhouse correction) and Tukey *post hoc* analyses to correct for multiple comparisons. Statistical analyses and graphical outputs were generated using GraphPad Prism 9 (GraphPad, San Diego, CA, USA).

Results

Participant characteristics

Of the cohort of 40 participants enrolled in the main vitamin C RCT, hospital mortality was 35% (n=14).[12] Of the 26 survivors, 18 (69%) enrolled in the 6-month QoL follow-up phase, with data for half of these participants captured at discharge. The baseline characteristics of the full cohort, survivors and the QoL sub-group are shown in Table 1. The median (IQR) age of the QoL participants was 65 (60, 71) and 61% were male. The predominant sources of sepsis were abdominal (50%), skin/soft tissue (22%) and blood (16%). The median (IQR) SAPS2 score was 49 (38, 58), APACHE-III score was 85 (73, 95) and SOFA score was 9.0 (6.8, 10).

Physical and mental health

The SF-36 questionnaire was used to assess the physical and mental health of the participants over the 6 months following discharge from hospital. All subscales were lower than New Zealand norms at discharge but improved over time, although bodily pain, role—emotional and mental health did not change significantly (Table 2). However,

Table 2: SF-36 findings for the total QoL cohort.

	Hospital discharge	30 days	90 days	180 days	P-value	New Zealand norms
	(n=9)	(n=18)	(n=17)	(n=18)		(n=12,378)
Physical function (PF)	31 (13, 49)	52 (41, 64)	60 (46, 75)	70 (57, 84)	0.001	86 (22)
Role—physical (RP)	3 (-4, 9)	19 (3, 36)	43 (23, 62)	61 (42, 80)	<0.001	86 (23)
Bodily pain (BP)	47 (14, 79)	69 (54, 84)	65 (48, 81)	76 (61, 92)	0.1	75 (24)
General health (GH)	38 (21, 55)	47 (34, 60)	59 (46, 71)	62 (51, 73)	0.002	75 (20)
Vitality (VT)	39 (20, 59)	51 (42, 61)	58 (46, 70)	67 (56, 78)	0.01	64 (18)
Social functioning (SF)	40 (15, 66)	55 (42, 68)	78 (67, 94)	87 (74, 100)	<0.001	88 (21)
Role—emotional (RE)	59 (21, 97)	67 (46, 87)	78 (61, 96)	91 (81, 100)	0.1	94 (15)
Mental health (MH)	67 (50, 84)	78 (68, 88)	83 (73, 92)	84 (75, 92)	0.1	82 (13)

Data represent mean and 95% CI. P-value is for trend over time (mixed effects model). New Zealand norms were from Frieling et al.[27] and represent mean (SD).
QoL = quality of life; SF-36 = Short Form-36.

even after 6 months, physical function, role—physical and general health appeared lower than New Zealand norms, whereas the emotional wellbeing parameters (vitality, social functioning, role—emotional and mental health) appeared comparable to New Zealand norms after 6 months. The physical component summary (PCS) was less than two-thirds of the New Zealand norm at discharge, while the mental component summary (MCS) was three-quarters of the New Zealand norm. Both the PCS and MCS improved significantly over time (p<0.006; Table 3).

Quality of life

At hospital discharge, 75–100% of the survivors had problems with mobility, self-care, usual activities, pain/discomfort and anxiety/depression, as determined by the EQ-5D (Table 4). Mobility, self-care and usual activities continued to improve over the 6-month follow-up period and became comparable to New Zealand norms (Figures 1A–C), while the subjective measures of pain/discomfort and anxiety/depression improved earlier and were better than population norms at 6 months (Figures 1D and E). The EQ-5D index score, a composite of the individual parameters, was observed to increase over time (p=0.04; Table 5). Similarly, the participant visual analogue scale (VAS) scores improved over time (p=0.003). There was a significant positive correlation between the EQ-5D index and VAS values (r=0.77 [0.64, 0.86], p<0.0001).

Cognitive function

Cognitive dysfunction remained unchanged from hospital discharge for 6 months (mean [95% CI] scores of 13 [6, 20] points at discharge, 11 [8, 14] at 30 and 90 days, and 10 [6, 15] by 6 months;

Table 3: Summary T-scores of self-reported physical and mental health measures for the SF-36v2.

	Hospital discharge	30 days	90 days	180 days	P-value	Population norm
	(n=9)	(n=18)	(n=17)	(n=18)		
Physical component summary (PCS)	31 (8)	37 (10)	41 (11)	45 (11)	<0.001	50 (10)
Mental component summary (MCS)	38 (12)	43 (10)	47 (11)	52 (10)	0.006	50 (10)

Data represent mean and SD. P value is for trend over time (mixed effects model).
SF-36v2 = Short Form-36, version 2.

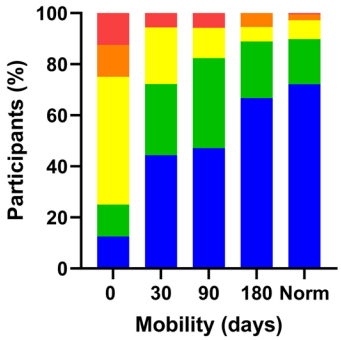
Table 4: Participant summary of self-rated physical and mental health measures as assessed by the EQ-5D.

	Hospital discharge	30 days	90 days	180 days	P-value	New Zealand norms
	(n=8)	(n=18)	(n=17)	(n=18)		(n=2,468)
Mobility	88	56	53	33	0.03	28
Self-care	75	28	6	11	0.01	9
Usual activities	100	67	35	28	0.004	30
Pain/discomfort	75	59	41	39	0.1	62
Anxiety/depression	75	33	33	28	0.08	46

Data represent percentage (%) with physical and mental health issues. P-value is for trend over time (mixed effects model). New Zealand norms were from Sullivan et al.[33]
EQ-5D = EuroQol 5 Dimension.

Figure 1: The proportion of participants with health problems for A) mobility, B) self-care, C) usual activites, D) pain/discomfort and E) anxiety/depression over 6-month period post-discharge. Problems were graded as none (blue), slight (green), moderate (yellow), severe (orange) or extreme (red). "Norm" is New Zealand norm values from Sullivan et al.[33]

A



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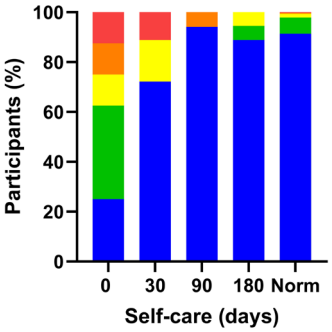

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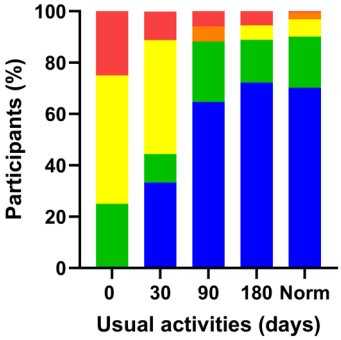

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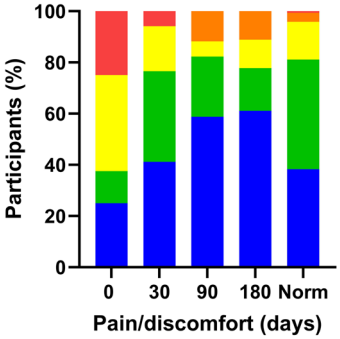

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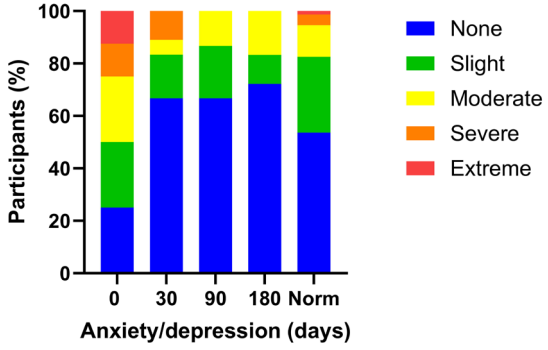


Table 5: The EQ-5D index and VAS scores.

	Hospital discharge	30 days	90 days	180 days	P-value	New Zealand norms
	(n=8)	(n=18)	(n=17)	(n=18)		(n=2,468)
EQ-5D index (%)	37 (11, 63)	61 (47, 75)	70 (53, 87)	76 (60, 91)	0.04	85 (24)
VAS (%)	51 (32, 69)	60 (47, 72)	71 (59, 82)	80 (72, 88)	0.003	75 (18)

Data represent mean and 95% CI. P value is for trend over time (mixed effects model). New Zealand norms were from Sullivan et al.[33] and represent mean (SD).
EQ-5D = EuroQol 5 Dimension; VAS = visual analogue scale.

p=0.6). The proportion of participants with a score >14 points was 30% at baseline and 33% at 6 months.

Effect of vitamin C intervention

Although short-term (4-day) intravenous vitamin C administration appeared to improve median SF-36 PCS scores post-discharge, these were not significantly different to placebo (Figure 2A). No significant difference between vitamin C and placebo was observed for MCS scores post-discharge (Figure 2B). Vitamin C intervention also did not have any effect on the EQ-5D index or VAS scores post-discharge (Figures 2C and D), or the individual physical and mental parameters (p>0.05). There was no significant effect of short-term vitamin C intervention on COBRA scores post-discharge relative to placebo (Figure 2E).

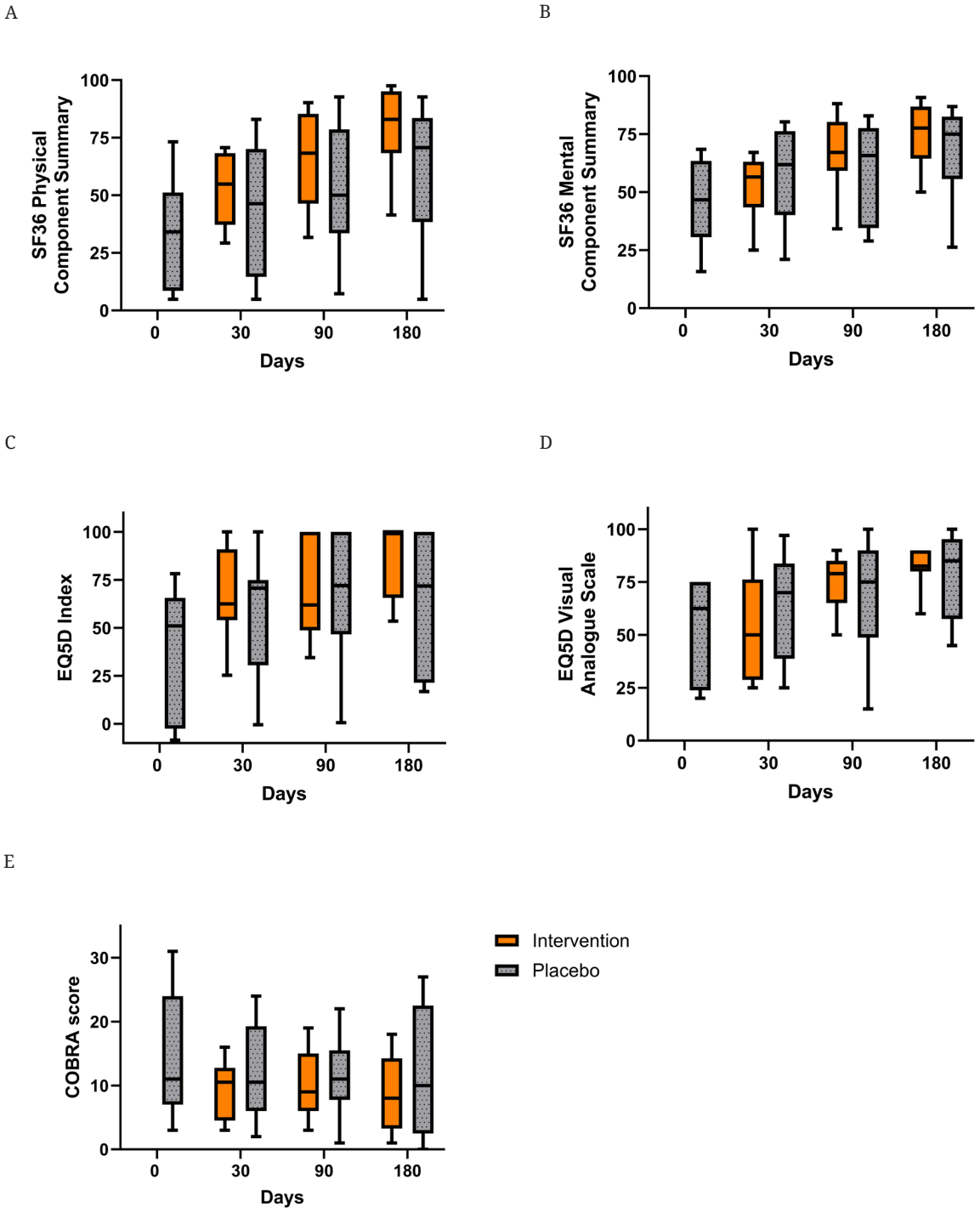
Discussion

This study is the first comprehensive and systematic assessment of health-related QoL and its various domains following ICU admission for survivors of sepsis in New Zealand. The study monitored the post-hospital discharge impact of physical, mental and cognitive issues on the health-related QoL trajectory of survivors of septic shock over a 6-month period. In agreement with Heyland et al.,[26] who assessed the QoL of 30 sepsis survivors after hospital discharge in Ontario using the SF-36 health domains, we observed dramatically lower physical and mental health subscale scores at discharge compared with New Zealand norms, with physical health generally scoring lower than mental health. Most of these scores improved over the 6-month follow-up period, although the physical function, role—physical and general health scores still appeared lower than population norms after 6 months. In contrast, the mental health scores had recovered to population norms within this time.

The SF-36 data was supported by EQ-5D data, which also showed a high proportion of physical and mental health issues at discharge, with improvements in mobility, self-care and usual activities to New Zealand norms within 6 months. Interestingly, the more subjective issues of pain/discomfort and anxiety/depression appeared to improve beyond New Zealand norms. This could reflect the small sample size and/or selection bias. Alternatively, subjective measures relate to perceived health and, following a severe illness, participants may feel they are in much better health relative to how they felt at discharge, resulting in higher scores than New Zealand norm populations, who have not experienced a life-threatening illness to compare their current subjective state against.[34] Other researchers have shown comparable EQ-5D results between survivors of sepsis and non-sepsis survivors,[11,35] although older patients in the sepsis group had a higher prevalence of problems.[35]

Survivors of severe sepsis can have substantial and long-term cognitive impairment,[36] and research suggests that the combination of cognitive complaints and depressive symptoms can negatively impact on health-related QoL.[37] We used the COBRA to assess cognitive dysfunction; this has not previously been used in an ICU cohort, although data exist for ~500 non-hospitalised adults.[37,38] Our septic cohort had a mean (SD) post-discharge COBRA score of 13 (10) relative to a non-hospitalised mean (SD) COBRA score of 8.5 (6.5).[38] Furthermore, 30% of the septic cohort had a COBRA score greater than 14, relative to 18% in non-hospitalised adults.[38] Cognitive impairment in the survivors of sepsis was still present at 6

Figure 2: Effect of vitamin C intervention on physical and mental quality of life and cognitive function post-hospital discharge. A) The physical component summary (PCS) comprised physical function (PF), role—physical (RP), bodily pain (BP) and aspects of general health (GH). B) The mental component summary (MCS) comprised general health (GH), vitality (VT), social functioning (SF), role—emotional (RE) and mental health (MH). C) EQ-5D index comprising mobility, self-care, usual activities, pain/discomfort and anxiety depression (converted to percentages). D) EQ-5D visual analogue scale (VAS). E) Cognitive function (COBRA) scores. Grey bars = placebo (n=7–10), orange bars = intervention (n=8). Day 0 data are not shown for the vitamin C arm as n=2. Bars represent median and 25th and 75th percentiles, and error bars the range.



months, and has been reported to persist for up to 8 years.[36] Thus, abnormal cognitive function appears to persist for significantly longer than subjective mood issues. Furthermore, the slow neuro-recovery, in combination with lower physical health, may impact on the survivor's ability to live independently.[36]

Pre-clinical studies suggest that vitamin C may act as a neuroprotective agent through improving biomarkers of neuroprotection, functional outcomes and mortality.[39] Although these results have not been translated to all human studies, the clinical trials used approximately one-tenth of the vitamin C doses relative to the animal studies. Thus, high-dose IV vitamin C may be anticipated to be more effective at preserving neurological function. However, the participants in the current trial who were randomised to 4 days of 100mg/kg/day intravenous vitamin C administration did not appear to have any improvement in post-discharge cognitive function relative to placebo participants, as was also reported recently with combination therapy.[40] Furthermore, there were no apparent effects of short-term vitamin C administration on post-discharge physical and mental health parameters as determined by the SF-36 and EQ-5D, as was also previously reported for intravenous hydrocortisone administration relative to placebo.[8] However, prior research in critically ill patients has indicated a rapid drop in vitamin C to baseline concentrations following withdrawal of intervention.[19,41] Thus, ongoing oral vitamin C supplementation following cessation of intravenous administration may be required to maintain adequate circulating concentrations to support normal vitamin C–dependent bodily functions.[42]

This research had several limitations, including the relatively small numbers of participants recruited to the QoL follow-up, although clear trends in QoL were still observed over time despite this. However, due to the small numbers, we were unable to correlate clinical parameters with QoL outcomes. Although this is the first study describing sepsis recovery in a New Zealand cohort, it is an ICU cohort, which is a treated rather than a true population of people with sepsis. Thus, the outcomes of the larger non-ICU population with sepsis may not be the same as reported in the current study. Another limitation was the use of COBRA to assess cognitive function of the participants as, to our knowledge, this has not previously been tested in ICU cohorts, being primarily used for participants with bipolar disorder. Nevertheless, it has previously been used for non-hospitalised adults.[37,38] A further limitation of the research was the inability to continue supplementing the participants with oral vitamin C or placebo following hospital discharge due to the main RCT protocol parameters.[12]

Overall, our QoL study provides novel descriptive findings relating to the trajectory of sepsis recovery in a New Zealand cohort, and highlights the long-lasting consequences of sepsis, emphasising the need for ongoing support post–hospital discharge to address the physical, mental and cognitive challenges faced by survivors. The participants had severe physical and mental health issues at hospital discharge, and although many subscales improved over the 6-month study period, particularly the mental health subscales, some physical health subscales remained below New Zealand norms. Cognitive dysfunction was worse than non-hospitalised adults, with a much higher proportion of post-septic participants having COBRA scores of greater than 14. Cognitive dysfunction persisted over the 6-month study period. Short-term intravenous vitamin C administration had no effect on the post–hospital discharge physical, mental or cognitive parameters, but future research should also focus on assessing the QoL measures of sepsis survivors who receive sufficient ongoing vitamin C administration to maintain adequate circulating plasma concentrations post–hospital discharge.

COMPETING INTERESTS
Nil.
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