

MANUSCRIPT TITLE

Determinants of health-related quality of life after intensive care: importance of patient demographics, previous comorbidity, and severity of illness

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Author's Contributions

JM, LS, and TSW obtained funding. DG, LS, and TSW conceived the study. NL, RL, DG, LS, and TSW designed the analysis. DG and RL conducted the analysis. DG, LS, and TSW wrote the manuscript. All authors reviewed manuscript drafts and approved the final version of the manuscript.

ABSTRACT

Objective

Intensive care (ICU) survivors frequently report reduced health-related quality of life (HRQoL), but the relative importance of pre-illness versus acute illness factors in survivor populations is not well understood. We aimed to explore HRQoL trajectories over 12 months following ICU discharge, patterns of improvement or deterioration over this period, and the relative importance of demographics (age, gender, social deprivation), pre-existing health (functional comorbidity index (FCI)), and acute illness severity (APACHE II score, ventilation days) as determinants of HRQoL and relevant patient-reported symptoms during the year following ICU discharge.

Design

Nested cohort study within a previously published randomised controlled trial.

Setting

Two ICUs in Edinburgh, Scotland.

Patients

Adult ICU survivors (N=240) who required more than 48 hours mechanical ventilation (MV).

Interventions

None.

Measurements and Main Results

We prospectively collected data for age, gender, social deprivation (Scottish Index of Multiple Deprivation), pre-existing comorbidity (Functional Comorbidity Index), APACHE II score, and days of mechanical ventilation (MV). HRQoL (Medical Outcomes Study Short Form version 2 (SF12 v2) physical (PCS) and mental (MCS) components scores) and patient-reported symptoms (appetite, fatigue, pain, joint stiffness and breathlessness) were measured at 3, 6, and 12 months. Mean PCS and MCS were reduced at all time points with minimal change between 3 and 12 months. In multivariable analysis increasing pre-ICU comorbidity count was strongly associated with lower HRQoL (PCS β = -1.56 (-2.44 to -0.68); p = 0.001; MCS β = -1.45 (-2.37 to -0.53); p = 0.002) and more severe self-reported symptoms. In contrast, APACHE II score and MV days were not associated with HRQoL. Older age (β 0.33 (0.19 to 0.47); p < 0.001) and lower social deprivation (β 1.38 (0.03 to 2.74); p = 0.045) were associated with better MCS HRQoL.

Conclusions

Pre-existing comorbidity count, but not severity of ICU illness, are strongly associated with HRQoL and physical symptoms in the year following critical illness.

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INTRODUCTION

ICU survivors report poor health-related quality of life (HRQoL) in the months and years following hospital discharge.(1–3) Rehabilitation trials testing numerous interventions during and after ICU have been ineffective at improving HRQoL and other measures of health status.(4–10) (11) When positive effects have been described, they have been limited to HRQoL sub-domains at time points that are of uncertain clinical significance.(5)(6)(7)(8)(9, 10)

Given these results, it is reasonable to assume that the interventions tested are ineffective and that greater knowledge of the underlying pathophysiology and the approaches used in future trials should be research priorities. However, it is also possible that the heterogeneous ICU populations included in trials include subgroups of patients that respond differently to interventions. Specifically, some patients may have refractory functional impairments, perhaps as a result of pre-ICU health that cannot be modified. These patients might mask important positive effects in other sub-populations.(12)(13)

The post-intensive care syndrome (PICS) conceptualises the direct effects of critical illness on physical and mental health, but the importance of pre-existing illness relative to the acute ‘hit’ of critical illness remains poorly understood. An improved understanding of the determinants of long term health following critical illness could improve the evaluation of interventions designed to improve recovery. The inclusion of HRQoL as a core outcome following critical illness highlights the need for a detailed understanding of this and related outcome measures.(14)

In a randomised trial of post-intensive care hospital based rehabilitation we recently found no effect on measures on functional status, HRQoL, or physical symptoms during 12

months follow-up.(5)(15). We hypothesised that this lack of effect might relate in part to pre-critical illness factors, a 'signal to noise' issue, whereby the 'noise' of non-modifiable pre-existing health may have dominated any 'signal' of effect in the trial. Our aims in this nested cohort study of the trial data were to describe trajectories of HRQoL over 12 months following ICU discharge; to identify patients whose HRQoL either deteriorated or failed to improve between 3 months and 12 months ICU discharge; to explore the relative importance of patient demographics, pre-critical illness health status, and critical illness severity as determinants of individual HRQoL trajectory after ICU discharge; and, to assess the consistency of associations in other patient centred outcomes we collected in the trial.

MATERIALS AND METHODS

This was a cohort study nested within a randomised trial of increased hospital-based physical rehabilitation and information provision for ICU survivors who required ≥ 48 hours of continuous mechanical ventilation (MV). Detailed trial inclusion/exclusion criteria have been published previously.⁽¹⁶⁾ Participants received either usual care or the intervention. As no treatment effects for HRQoL or patient-reported symptoms were found, a single cohort was constructed from the trial database to address the following research questions: What were the cohort level trajectories of PCS and MCS between 3 months and 12 months after ICU discharge? What proportions of patients showed no clinically important improvement of PCS and MCS between 3 and 12 months? Which factors were most strongly associated with HRQoL at 6 and 12 month post-ICU discharge? Which factors were most strongly associated with patient-reported symptoms at 12 months post ICU discharge? This study was approved by the Scotland A Research Ethics committee. Participants or their surrogate decision makers provided written informed consent.

Outcome measures

For HRQoL, the Medical Outcomes Study Short Form 12 version 2 (SF12v2), including the Physical Component Score (PCS; range 0-100) and Mental Component Score (MCS; range 0-100) calculated using US-derived co-efficients.⁽¹⁷⁾ Patient-reported physical symptoms of appetite, fatigue, pain, joint stiffness and breathlessness were measured on a visual analogue scale of 10cm in length ranging from 0 (no symptoms at all) to 10 (worse symptoms imaginable). As per the trial protocol, the trial aimed to measure these outcomes for all surviving patients at 3, 6, and 12 months post-randomisation.

Exposures

We selected variables from the trial database to best represent demographics, pre-existing comorbidity burden, and critical illness severity and duration. The number of variables did not exceed recommended maximums to prevent overfitting.(18)

Patient characteristics: We used age, gender, and social deprivation. Social deprivation was measured using the Scottish Index of Multiple Deprivation (SIMD), a post-code based deprivation ranking of each of 6,976 geographical areas within Scotland. These are described in quintiles ranging from 1 (most deprived) to 5 (least deprived).(19)

Pre-existing comorbidity burden: We used the Functional Comorbidity Index (FCI) assessed at study entry by review of medical records, and by discussion with patients and families. This validated measure is based on 18 comorbidity items with higher scores indicating more comorbidities.(20, 21)

Features of acute illness severity: We used the APACHE II score,(22) and days of MV.

Immediate post-ICU discharge physical status: We measured the Rivermead Mobility Index (RMI), and the physical assessment of the Subjective Global Assessment of Nutrition (SGA) at enrolment (ICU discharge). The RMI is a hierarchical mobility index ranging from 0 (bedridden) to 15 (able to run).(23) The SGA is a subjective clinical assessment of nutritional status based on signs of fat loss, muscle wasting, and oedema measured on a scale of 1 (well nourished) to 3 (severely malnourished).(24)

Analysis

Statistical analysis was conducted using SPSS (IBM Corp. Released 2012. SPSS Statistics for Mackintosh, version 21.0, Armonk, NY; or Released 2016. SPSS Statistics for Mackintosh, version 24.0, Armonk, NY). Sankey plots were created using SankeyMATIC (<http://sankeymatic.com/build/>).

Cohort level trajectories of PCS and MCS between 3 months and 12 months after ICU discharge

PCS and MCS trajectories were plotted for individual patients. Mean (95% confidence interval (CI)) PCS and MCS were plotted to summarise cohort level trajectories. Comparison between PCS and MCS at 3 and 12 months was made using paired t tests.

Proportions of patients that showed no clinically important improvement of PCS and MCS between 3 and 12 months

We defined a minimum clinical important difference (MCID) in PCS and MCS as $>\pm 5$ points (consistent with published literature) and used Sankey plots to illustrate groups of patients that improved, deteriorated, or remained static between 3 months and 12 months.⁽²⁵⁾ To explore floor and ceiling effects in this analysis, we re-plotted the Sankey plots for each quartile of HRQoL score at baseline.

Factors most strongly associated with HRQoL at 6 and 12 months after ICU discharge

We used bivariate unadjusted linear regression to examine univariate associations between the exposure variables and HRQoL at 6 and 12 months following ICU discharge, and multivariable linear models to explore the relative importance of each variable. For each outcome variable, two models were fitted. The first model excluded physical status measured at ICU discharge (SGA and RMI at ICU discharge; model 1) on the assumption that these

variables encompassed the effects of the acute illness and the pre-morbid physical function and would not add additional information. As a sensitivity analysis, the second model (model 2) included the RMI and SGA nutrition at ICU discharge to explore the possibility that immediate post-ICU physical status might more strongly account for long-term HRQoL. RMI was log transformed ($\ln(1+\text{RMI})$) prior to analysis.

Risk factors most strongly associated with patient-reported symptoms at 12 months post ICU discharge

To assess whether consistent associations were also observed when patient symptoms were used in place of HRQoL, we repeated the regression analysis for each of the 5 patient-reported symptoms (appetite, fatigue, pain, joint stiffness, and breathlessness) at 12 months.

Missing data

We undertook a complete case analysis. To assess whether cases with missing data were likely to be different from those included, baseline characteristics were compared between missing and included cases.

RESULTS

Of the 240 patients enrolled in the RECOVER study, 228, 220, and 218 patients were alive at 3, 6, and 12 months respectively (study flow diagram in figure E1 in the electronic supplement) and HRQoL data was available for 197/228 (86%), 165/220 (75%) and 155/218 (71%) of these survivors. Baseline characteristics are shown in table 1. Patients with missing data were similar to included patients in respect of pre-existing health, baseline demographics, and severity of illness (see online electronic supplement; table E8).

Cohort level trajectories of PCS and MCS between 3 months and 12 months after ICU discharge

Individual patient plots showed marked heterogeneity over time for both HRQoL components (see figures E2-E3 in the electronic supplement). At cohort level, mean PCS was reduced compared to population norms (where population norm is 50 on each scale) at all time points (Figure 1(A) and table 2). The PCS increased by a statistically significant but clinically small amount between 3 months and 12 months, with an overall change less than the pre-defined MCID of 5 (mean difference (95% CI): 2.3 (0.6 to 3.9); $p=0.006$). MCS was also reduced compared to population norms but higher than the PCS at each time point. Mean MCS did not change between 3 and 12 months (Figure 1(B) and table 2) (mean difference (95% CI): 0.2 (-1.8 to 2.1); $p=0.87$). These cohort level data suggested plateauing of both measures by 3 months, with little subsequent change.

Proportions of patients that showed no clinically important improvement of PCS and MCS between 3 and 12 months

147 patients had complete PCS and MCS data at 3 and 12 months. Ninety-four patients (63%) had no clinically significant improvement in PCS between 3 and 12 months (table E1 (electronic supplement) and figure 1 (Panel C)). One-hundred and one patients (69%) had no clinically significant improvement in MCS (figure 1 (Panel D)). In the sensitivity analysis, 50%, 58%, 70% and 77% of patients in quartiles 1 (lowest HRQoL), 2, 3, and 4 of PCS at baseline had no clinically important improvement; 44%, 66%, 65% and 97% of patients in quartiles 1, 2, 3, and 4 of MCS at baseline had no clinically important improvement.

Risk factors most strongly associated with HRQoL at 6 and 12 months after ICU discharge

Adjusted model 1 co-efficients (excluding RMI and SGA) at the 6-month time point are shown in table 3. Unadjusted co-efficients and adjusted model 2 co-efficients (including RMI and SGA) are shown in table E2 (6 months) and table E3 (12 months) in the electronic supplement. In the adjusted models, a higher comorbidity count was strongly associated with lower (worse) PCS and MCS at 6 and 12 months. Critical illness related variables were not associated with either PCS or MCS at either time point. Examining other patient characteristics, there was a strong association observed between increasing age and higher (better) MCS at 6 and 12 months. There was also an association between higher social class (higher SIMD quintile (lower deprivation)) and higher (better) MCS at 6 months but not 12 months. In the sensitivity analyses, the inclusion of measures of early post-ICU discharge physical status (RMI and nutrition) did not significantly alter the observed effect sizes

To illustrate the impact of increasing physical comorbidity on HRQoL trajectory, we plotted HRQoL trajectories according to sub-groups of patients with different comorbidity counts prior to ICU admission. This clearly showed that as the numbers of comorbidities present pre-ICU increased, the PCS and MCS were lower during the 12 months following ICU

discharge and tended to follow a flatter trajectory indicating lack of improvement (figure 2 and tables E4-6 (electronic supplement)). This was most marked for PCS.

Risk factors most strongly associated with patient-reported symptoms 12 months post ICU

discharge

Higher comorbidity count was independently associated with higher (worse) appetite, fatigue, pain, joint stiffness, and breathlessness symptom scores (table E7; online electronic supplement). Increasing SIMD quintile (lower deprivation) was associated with lower pain scores. Neither of the acute illness severity factors (APACHE II score or duration of MV) were associated with any of the symptoms. The observed co-efficients were not affected by nutrition and baseline RMI when tested in the sensitivity analysis, even though RMI and nutrition were associated with some of the symptom outcomes: Lower RMI (poorer mobility) at baseline was associated more severe joint stiffness during follow up. Poorer nutritional status on subjective assessment was associated with higher pain and fatigue scores during follow up.

DISCUSSION

We report a secondary analysis of trial data exploring trajectories and determinants of HRQoL and physical symptoms during 12 months of follow-up after critical illness. At cohort level PCS and MCS were below population means and did not change by a clinically important amount between 3 months and 12 months. Specifically, around two thirds of patients showed no clinically important improvement in MCS and PCS (≥ 5 points) between 3 and 6 months, even among the quartiles with lower HRQoL at 3 months. In multivariable analysis, pre-existing comorbidity count emerged as the most important predictor of long term HRQoL outcome. Patient demographics, measures of critical illness severity, and early post critical

illness physical status were not significant predictors of long term physical HRQoL once pre-existing comorbidity was taken into account. Recovery of physical function was most consistent in patients without pre-ICU comorbidity or with lower co-morbidity counts. The almost identical findings for a range of patient reported symptom scores reflecting patient health and well-being provide indirect validation for these findings.

Strengths of our study include the use of an externally valid prospectively included sample of ICU survivors from a randomised trial, but caution is still advised when extrapolating to other ICU cohorts. Exposures and outcomes were measured prospectively using valid tools. In particular, comorbidity count was collected prospectively in all patients at the time of enrolment by careful review of medical notes, and direct questioning of patient relatives; therefore, the accuracy of the FCI comorbidity is likely to be high. Assessment of illness severity factors was complete, and used measures that are known to affect short-term ICU outcomes.

Several limitations should be noted. A power calculation was not conducted making it possible (but unlikely given the small confidence intervals) that small sample size could explain the lack of association between critical illness severity and HRQoL. Missing data may have biased the analysis despite our included patients being similar to those without complete outcome data across all baseline variables measured. SF12v2 was used in preference to the more detailed SF-36 for pragmatic reasons (taking less time and concentration to complete) to reduce attrition bias, but may have reduced the resolution of our analysis. The strong relationship between severe subjective malnutrition and less severe physical symptoms is difficult to explain but could relate to the limitations of the SGA measure in oedematous post-ICU patients where signs of malnutrition may be masked by oedema. Finally, other factors such as social integration and family support in the months following

ICU discharge are known to be associated with HRQoL and may have been the cause of (or consequence of) reduced HRQoL in our patients. We were unable to explore this further in our study.(26)

Previous work has shown that ICU survivors have reduced HRQoL with minimal change after ICU, especially after 3 months post hospital discharge(1–3). Our data furthers the understanding of patient HRQoL trajectories at population level by showing that between 3 and 12 months only a minority have clinically important improvement, with the majority remaining static or deteriorating over time. Importantly, these patterns were evident irrespective of the HRQoL quartile at 3 months, with many patients in the lowest quartiles reporting no subsequent improvement. Previous studies have implied that incomplete long term recovery may be a direct consequences of critical illness, comprising the ‘post-intensive care syndrome’. However, most lacked reliable pre-critical illness comorbidity, HRQoL, or other data to assess the relative contribution of pre-existing health to post-ICU outcomes. Orwelius and colleagues used questionnaires administered to ICU patients surviving 6 months from ICU discharge to retrospectively assess pre-ICU health status, with a 59% response rate. Their analysis suggested pre-existing disease was a strong independent determinant of HRQoL outcomes, but was potentially subject to recall and response bias.(27) A more recent sub-study of patients aged 70 years or older, who participated in a larger cohort study of functional recovery but required an ICU admission, explored a range of potential determinants of return to pre-critical illness functional status. In this analysis, pre-ICU impairments of hearing and vision were strongly associated with poor functional outcome at 6 months, but comorbidity count and ICU related factors were not.(28) Our prospective study sampled a general mixed ICU population across all adult age groups, and provides strong

evidence for the importance of pre-ICU comorbidity as a major determinant of post-ICU HRQoL beyond the first 3 months post-ICU discharge.

Our findings add to a growing body of research highlighting pre-ICU health as a key determinant of important ICU outcomes including mortality(29) and healthcare resource use (30) in addition to functional recovery and HRQoL. This has implications for future trial design. In trials seeking to improve post-ICU HRQoL for example, more comorbid patients may have limited or no responsiveness to the trial intervention, which could mask important effects in less comorbid groups. In future trials and outcomes research we believe our data show that careful consideration of pre-existing health status is essential when HRQoL or similar patient-centred measures are key long-term outcomes, as has been recently recommended.(14) These factors need to be considered when defining study populations, which baseline data to collect, and how statistical adjustment is undertaken during analyses. Failure to consider these issues may undermine power calculations and mask important clinical effects in less comorbid patients.(12)

CONCLUSIONS

In a prospectively studied sample derived from a post-ICU rehabilitation trial, HRQoL was reduced in ICU survivors. Many patients failed to experience clinically important improvement in HRQoL between 3 and 12 months. Pre-critical illness comorbidity rather than features of the critical illness were the strongest predictors of survivors' HRQoL and self-reported physical symptoms during the 3 to 12 months following ICU discharge.

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FIGURE LEGENDS

Figure 1

Health-related quality of life trajectory between 3 and 12 months after ICU discharge. Panels A and B show cohort level data with mean (95% CI) for Physical Component Score (PCS) of the Short Form 12 version 2 (SF12v2) (A) and Mental Component Score (MCS) of SF12v2 (B). Dashed lines indicate the population norm of 50 for both scores. Panels C and D show the subset of patient with SF12v2 measured at both 3 months and 12 months to demonstrate subgroups of patients that improved or deteriorated by more than the minimal clinical important difference (5 points) on each scale between 3 and 12 months. Plots are stratified by quartile of PCS (C) or MCS (D) at 3 months. Panels A and B: Whole cohort data. n at 3, 6 and 12 months: 197, 165, and 155 respectively. Panels C and D: subset of patients with PCS/MCS data at 3 months at 12 months: n=147.

Figure 2

Health-related quality of life trajectory between 3 and 12 months after ICU discharge for patients with data at all time points. Panels show data for Physical Component Score (A) and Mental Component Score (B) stratified according to the number of baseline comorbidities. Mean (standard error of the mean). n=137.