Perioperative Research into Memory (PRiMe): Cognitive impairment following a severe burn injury and critical care admission, part 1.

Edward J R Watson[a,b]*, Klaraá Nenadlová[a,c], Olivia H Clancy[a], Mena Farag[a], Naz A Nordin[a,d], Agnes Nilsen[a,c], Ashley R T Mehmet[a,c], Ahmed Al-Hindawi[a,b], Sundhiya Mandalia[a,b], Lisa M Williams[a], Trudi L Edginton[c,e], Marcela P Vizcaychipi[a,b]

[a] Magill Department of Anaesthesia, Pain Medicine and Intensive Care, Chelsea and Westminster Hospital NHS Foundation Trust, London, U.K.

[b] Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, U.K.

[c] Psychology Department, Westminster University, London, UK

[d] Department of Anaesthesia, Watford General Hospital, West Hertfordshire Hospitals NHS Trust, U.K.

[e] Department of Psychology, City, University of London, U.K.

*Corresponding author at: Magill Department of Anaesthesia, Pain Medicine and Intensive Care Medicine, Chelsea and Westminster Hospital NHS Foundation Trust, 369 Fulham Road, SW10 9NH, London, U.K.
edward.watson@imperial.ac.uk

Abstract

Introduction: An investigation into long-term cognitive impairment and Quality of Life (QoL) after severe burns.

Methods: A proof of principle, cohort design, prospective, observational clinical study. Patients with severe burns (>15% TBSA) admitted to Burns ICU for invasive ventilation were recruited for psychocognitive assessment with a convenience sample of age and sex-matched controls. Participants completed psychological and QoL questionnaires, the Cogstate® electronic battery, Hopkins Verbal Learning, Verbal Fluency and Trail making tasks.

Results: 15 patients (11M, 4F; 41 ±14 years; TBSA 38.4% ±18.5) and comparators (11M, 4F; 40 ±13 years) were recruited. Burns patients reported worse QoL (Neuro-QoL Short Form v2, patient 30.1 ±8.2, control 38.7 ±3.2, p=0.0004) and cognitive function (patient composite z-score 0.01, IQR -0.11 - 0.33, control 0.13, IQR 0.47 - 0.73, p=0.02). Compared to estimated premorbid FSIQ, patients dropped an equivalent of 8 IQ points (p=0.002). Cognitive function negatively correlated with burn severity (rBaux score, p=0.04). QoL strongly correlated with depressive symptoms (Rho=-0.67, p=0.009) but not cognitive function.

Conclusions: Severe burns injuries are associated with a significant, global, cognitive deficit. Patients also report worse QoL, depression and post-traumatic stress. Perceived QoL from cognitive impairment was more closely associated with depression than cognitive impairment.

Keywords: Severe burns; critical illness; cognitive impairment; mental health; Quality of Life

1. Introduction

The survival rates of patients requiring intensive care unit (ICU) admission following severe burns injuries continue to improve with advances in critical care medicine and burns management[1–5]. Admission to ICU is associated with physical, psychological and cognitive sequelae, which are in turn associated with a multi-faceted reduction in Quality of Life (QoL). This spans physical, mental and social domains, with many severe burns patients being unable to return to work within a year of discharge[6–8].

One of the most distressing problems affecting patients following discharge from ICU is that of long-term cognitive impairment (LTCI)[9–17]. This affects up to two thirds of patients[18] and can range in magnitude from subtle to major deficits in executive function and working memory. Cognitive deficits stemming from a wide range of medical conditions are known to have a significant impact on QoL[19–24]. It has been recognised after electrical injury, however there is limited research into ICU LTCI following severe general burns[25–28] and a dearth of research into any effect this may have on QoL. Patients with major burns encounter a markedly greater magnitude of inflammatory and hypermetabolic sequelae than general ICU cohorts[29,30]. In addition to this endogenous biochemical milieu, severe burns necessitate multiple surgeries and accompanying general anaesthetics to treat their injuries, and attract numerous nosocomial infections[31,32]. Anaesthesia[33–37] and pro-inflammatory states[38,39] are also known to be associated with LTCI. As such, severe burns patients admitted to ICU are a unique subgroup of patients that may be at particularly high risk of LTCI.

It is now accepted that the brain mounts an inflammatory response following local and systemic insults[30,40–42]. There is evidence suggesting that inflammatory mediators and the immune system play a significant role in adult hippocampal neurogenesis and memory formation in both health and disease, although the processes involved in immune activated neuroplasticity are not fully understood[43]. With the use of advanced neuroimaging techniques it is possible to identify surrogate markers of neuroinflammation in specific brain regions associated with memory formation in vivo[44,45].

This study has been performed in two parts due to the breadth of data collected. In part one we set out to look for long-term neurocognitive sequelae after a severe burns injury and any resulting impact on QoL. In part two, we look for any corresponding evidence of neuroinflammation with the use of multi-parametric Magnetic Resonance Imaging (MRI), including: diffusion weighted imaging, MR spectroscopy and resting-state fMRI.

2. Materials and Methods

This was a proof of principle, cohort design, prospective, observational clinical study. ClinicalTrials.gov ID: NCT03242395

2.1. Ethics approval

Ethics approval was granted by the Surrey Borders Research Ethics Committee on the 30th January 2014 (Reference 14/LO/0049). Fully informed written consent was received from all participants in accordance with the UK Good Clinical Practice code of practice.

2.2. Recruitment and demographics

All patients admitted to the Chelsea and Westminster Hospital Burns Intensive Care Unit (BICU) between 2004 and 2015 were reviewed and considered for inclusion in this trial. Patients were also recruited through burns charities such as the Katie Piper Foundation. Recruitment ran over a two-year period from April 2014 until April 2016. Collateral information gathered included: age, sex, years of education, employment history, past medical history and the date, mechanism and size of burn. Burn severity and comorbidities were quantified by use of the revised Baux (rBaux) score and the Charlson Comorbidity Index (CCI) respectively[46,47].

A convenience sample of comparators was also recruited. The patients were asked to select a family member of the same sex and similar age for the comparator group. If no suitable kin was available then comparators were recruited via poster advertisements in the burns outpatient waiting room. After initial contact via email or telephone, volunteers were invited to attend the research department. Subsequent to providing written informed consent, participants underwent neurocognitive testing and were individually matched for age, sex and National Adult Reading Test (NART) derived Full-Scale IQ (FSIQ). The closest matches were included in the analysis and went on to have MRI scans in part two of the study.

2.3. Inclusion and exclusion criteria

All adult patients admitted to a BICU within the previous ten years (at the time of testing), who had been intubated and ventilated, and with burns greater than or equal to 15% total body surface area (TBSA) were screened for inclusion in this study.

Exclusion criteria included: BICU admission for illnesses other than burns (e.g. Toxic Epidermal Necrolysis Syndrome); evidence of head trauma; known substance misuse or alcohol excess; inability to understand plain verbal or written English; those receiving formal psychiatric treatment; those held under the Mental Health Act, or if their psychological health was deemed to be at risk from inclusion in the study (as assessed by the supervising clinical psychologist). In addition, contraindications to MRI were also contraindications to study inclusion.

2.4. Quality of Life

QoL was assessed using the Euro QoL 5 Dimensions (EQ5D) questionnaire, the Instrumental Activities of Daily Living (iADL) scale and the National Institute of Health Neuro-QoL Short Form version 2 (NIH Neuro-QoL SF v2).

2.5. Mental health

Three mental health domains were assessed in this study as confounding factors for cognitive impairment and QoL: anxiety, depression and post-traumatic stress. The Patient Health Questionnaire (PHQ-9) and Beck Depression Index II (BDI II) are self-report inventories assessing the presence and severity of symptoms of depression. Higher scores indicate greater depression. In the same manner, the Trauma Screening Questionnaire (TSQ) reports symptoms of post-traumatic stress and the Generalised Anxiety Disorder 7 (GAD- 7) and Beck Anxiety Inventory (BAI) assess symptoms of anxiety. These tests have established validity and reliability[48–56]. Patients with known psychosis were not included in this study, but patients were re-screened during testing through use of the Clinician-Rated Dimensions of Psychosis Symptom Severity scale.

2.6. Cognitive assessment

The cognitive domains assessed included: learning (visual and verbal) and memory (working memory, immediate and delayed recall, retention, recognition discrimination), attention and processing speed, executive function, language (semantic and switching fluency). The following validated cognitive tests were used to assess these domains: the Hopkins Verbal Learning Test (HVLT), Trail Making parts A and B (TMA, TMB), semantic and switching verbal fluency (SeF, SwF), as well as the Cogstate® computerised battery: Identification speed (ID), Detection speed (DT), One Card Learning accuracy (OCL), One Back test accuracy (ONB), Two Back test accuracy (TWB), International Shopping List total correct answers (ISL) and Groton Maze Learning total errors (GML)[57]. Premorbid FSIQ was estimated using the NART[58,59]. The NART is a mainstream tool that has been validated in a wide variety of cognitive disorders, from dementia to schizophrenia to traumatic brain injury, and has been shown to remain stable over time[59–62]. All neurocognitive tests were administered in a quiet room with a supervising clinician.

2.7. Statistical analysis

According to our power calculations, a sample size of 36 patients was indicated to identify long-term neurocognitive deficits following admission to BICU. However, a target of 10-26 patients for identification of neuroinflammatory changes by using MRI would suffice[44,45,63–65].

Parametric data are presented as means and standard deviations and non-parametric data are presented as medians and interquartile ranges. Continuous parametric data were analysed using the Student t-test (STT) and associations were tested for using the Pearson's correlation coefficient. Non-parametric data were analysed using the Mann Witney U test (MWUT) and associations were tested for using Spearman's rank correlation coefficient. All p-values presented are one tailed unless otherwise stated and statistical significance is defined as $p<0.05$.

EQ5D domain data was split into binary outcomes (1 = no reduction in QoL domain, 2 or 3 = reduction in QoL domain) and analysed with the Fisher's Exact test (FET). The Cogstate® tests include population means and standard deviations from which z-scores can be calculated. A composite cognitive score was produced from the median of the z-scores for each participant. This composite score was used to compare the two groups and to test for an association between cognitive function and burn severity.

The comparison group was not successfully matched for premorbid IQ and consequently the patient group was also tested against population data in three ways:

- The proportion of patients scoring Very Poor in at least two tests, a more stringent version of a common methodology used in POCD and similar ITU LTCI studies[33,66–68].
- The cognitive results were categorised according to standardised descriptor outcomes (Very Poor to Superior performance ranges) and parametric distribution was confirmed. The total number of results in the Very Poor (>2SD below the mean) performance range for the patient group was tested against that expected for a normal distribution with a Chi Squared test.

- The difference between premorbid FSIQ z-score and the Cogstate composite z-score was tested to determine if there was a change in IQ after injury.

3. Results

3.1. Recruitment and demographics

A total of 15 patients were recruited into the study (see figure 1), including 11 men and 4 women, with a mean age of 40.5 ±13.8 years and mean estimated premorbid FSIQ of 108 ±12 (half a standard deviation above the mean). The mean burn size was 38.4 ±18.5% TBSA. Three patients had documented inhalational injuries, resulting in a mean rBaux score of 79.4 ±18. No patients experienced a cardiac arrest or head injury as part of the injury, two patients reported transient loss of consciousness. The median interval between injury and neurocognitive assessment was 2.68 years (IQR 2.05-4.55).

None of the patients were willing to provide contacts for the control group. Reasons provided included non-availability or desire for privacy. The 15 age- and sex-matched comparators comprised 11 men and 4 women with a mean age of 39.9 ±12.9 years and mean estimated premorbid IQ of 116 ±8. They had a higher NART FSIQ than the patient group (STT p=0.016) but there were no significant differences in age or sex. One control had a recent road traffic accident with ensuing long ICU stay, this was deemed a significant confounding factor and his data was replaced with that of another. There was no significant difference in CCI scores between the groups and both had extremely low levels of comorbidity (patient median 0, IQR 0-0.5, comparator median 0, IQR 0-0, Mann Whitney U test p>0.05).

There was a statistically and clinically significant difference in level of education between the groups (patient mean 14.5 ±4 years, comparator mean 18 ±2 years, Student t test, p= 0.024), which is reflected in the premorbid FSIQ scores. Three of the injuries were work-related.

3.2. Quality of Life

The patient group reported a worse QoL on the EQ5D (patient median index value 0.767, IQR: 0.7-1; comparators median 1, IQR 1-1, MWUT p= 0.007). The patients had worse EQ5D scores in four of the five domains: usual activities (7/15 vs 0/15, FET p=0.01), pain/discomfort (10/15 vs 2/15, FET p=0.01), mobility (4/15 vs 0/15, FET p=0.049), and self-care (4/15 vs 0/15, FET p=0.049) (see figure 2). The fifth domain (Anxiety/depression) was not significantly different between the groups (7/15 patients vs 2/15 comparators, FET p>0.05). They also reported lower EQ5D visual analogue scale scores (patient mean 70% ±23.4, comparator mean 84% ±7.37, STT p=0.04).

A significant drop in cognitive Quality of Life was found on the Neuro-QoL in the burn group (patient mean 30.1 ±8.2, comparator mean 38.7 ±3.2, STT p=0.0004). There was still no correlation between the Neuro-QoL results and either the absolute cognitive score or the relative drop in cognition from baseline. However there was a significantly correlation with the BDI-II (Spearman's Rho = -0.67, p= 0.009).

There was no difference in iADL score (all participants scored the maximum score of 6).

3.3. Mental Health

The patient group had higher depression symptom scores for both the PHQ-9 (patient median: 6, IQR 1.5-13.5, comparator median: 1, IQR 0.5-1.5, MWUT p=0.01) and BDI-II (patient median 15, IQR 9.5-23.5; comparator median 3, IQR 1-7.5, MWUT p=0.005). They also reported higher traumatic stress symptoms in the TSQ (patient median: 3, IQR 1-6.5, comparator median 0, IQR 0-1.5, MWUT p=0.01). There was a non-significant rise in both the BAI (patient median 5, IQR 2-9, comparator median 2, IQR 1.5-3.5, MWUT p>0.05) and GAD-7 (patient median 3, IQR 0.5-9.5, comparator median 1, IQR 1-2, MWUT p>0.05) (see figure 3).

The Clinician-Rated Dimensions of Psychosis Symptom Severity scale showed a statistically significant difference between the groups (patient median 2, IQR 0.25-4, comparator median 0, IQR 0-1, Mann-Whitney U test p=0.001). Participants did not accrue points in any domains except for those of depression and cognitive impairment.

QoL outcomes (EQ5D total score) were strongly associated with each of the mental health questionnaires: PHQ-9 (Spearman's rho 0.78, p=0.0007), BDI-II (Spearman's rho 0.71, p=0.003) GAD-7 (Spearman's rho 0.80, p=0.0004), BAI (Spearman's rho 0.78, p=0.0007) and TSQ (Spearman's rho 0.70, p=0.004).

3.4. Cognitive assessment

The composite z-score for the patients (median 0.01, IQR -0.11 - 0.33) was significantly lower than that of the comparison group (median 0.47, IQR 0.13 - 0.73), MWUT p = 0.015. A negative correlation was found between the composite z-scores and rBaux score (Spearman's Rho=0.54, p=0.039) suggesting that cognitive function was worse with larger burns. The patient group performed worse in all of the tests, reaching statistical significance in six of the seventeen cognitive tests (see table 1). These spanned multiple domains, including working memory (ONB), delayed recall (HVLT), attention (TMA, ID), executive function (TMB) and language (semantic fluency). Raw scores are provided in table 1 below; statistical tests were performed on age- and education- adjusted conversions where population data was available.

The cognitive test results were categorised into 'Very Poor' to 'Superior'. The categorical results were normally distributed. The patients scored more than two standard deviations below the mean in 23 of the 255 tests performed. This was over three times greater than expected for a normal distribution (observed: 23, expected: 7, Chi squared p=0.003) (see figure 4). The comparator group was also normally distributed, albeit with a slight skew toward High Average performance reflecting their NART FSIQ scores. There was no disparity between the number of observed (7) and expected (7) results in the Very Poor performance range for the comparators. Six of the patients (40%) scored more than two standard deviations below the mean [Very Poor] in at least two of the cognitive tests, a threshold for cognitive impairment in many ITU and POCD studies.

Finally, the patients' mean estimated premorbid FSIQ was 108 (0.53 standard deviations above the population mean). This was also half a standard deviation above the Cogstate composite z-score, effectively representing an estimated drop of 7.5 IQ points from their baseline (Student t test p=0.017).

4. Discussion

This clinical study found that two years after a severe burns injury, patients demonstrated a significant deficit in cognitive function from baseline. Patients also reported an increase in depressive and post-traumatic stress symptoms with an associated reduction in Quality of Life.

4.1. Quality of Life

Cognitive impairment after a severe burn injury, as well as its effect on Quality of Life were issues brought to us by our patients and were the primary motivation for this study. We have demonstrated that both cognition and cognitive QoL are worse after a severe burn. As such, the finding of a lack of correlation between these two outcomes was quite unexpected. It is readily understandable that the iADL and EQ5D might not correlate with cognition. These tools measure specific outcomes (e.g.: mobility, self-care, pain/discomfort, mental health) but neither tool includes domains that inquire about cognitive function[69]. Even in populations with severe cognitive impairment, a lack of correlation between cognitive function and EQ5D score has been demonstrated[70].

However, despite the Neuro-QoL SF v2 specifically targeting cognitive symptoms, it also demonstrated a lack of correlation with cognitive function. A disconnect between actual and perceived impairment has been noted previously in the literature. Newman et al. found that self-reported post-operative cognitive dysfunction (POCD) was correlated with depressive symptoms but not with objective impairment[71]. Our results mirror this finding with a strong correlation between perceived cognitive function (Neuro-QoL) and depressive symptoms (BDI-II), but not between perceived cognitive function and cognitive ability (Cogstate z-score) or cognitive decline (the discrepancy between premorbid FSIQ z-score and Cogstate z-score).

We speculate that this indicates a measurement issue rather than proof of the null hypothesis. Quality of Life is a human construct and has a particularly nebulous quality. Common HRQL tools seek to define QoL through impact on daily function. We have demonstrated a reduction in actual cognition. The basic abilities that were measured are employed ubiquitously on a daily basis. A priori, there is a reduction in Quality of Life, even if the magnitude is not measurable with the tools used.

However, it would appear that the Neuro-QoL SF v2 was poorly sensitive for cognitive QoL in this cohort and had low discrimination from depressive symptoms. Patients with high levels of depressive symptoms may have an accentuated perception of cognitive impairment when it was present, or potentially false perceptions of impairment in its absence. Irrespective of the cause, the discrepancy between actual and perceived cognitive impairment was overshadowed by the impact of depression in this scenario. Secondarily, the Neuro-QoL SF v2 has a limited scope for the impact of cognition on QoL. There were no domains targeting the social and emotional aspects of cognitive impairment, which may have been salient features for the burns cohort.

4.2. Mental Health

Our results concur with Logsetty et al., revealing a significant rise in depressive and post-traumatic stress symptoms compared to a comparison group, alongside a non-significant rise in anxiety symptoms[72]. High levels of psychological symptoms are found commonly in burns cohorts, though

this may in part represent low pre-injury mental health. This has been reported in several large studies investigating long-term psychological symptoms after burns injuries[73–75], including BICU populations[76]. High depression and traumatic stress scores correlate strongly with poor QoL.

Participants reported high levels of irritation (PHQ-9, GAD-7, BDI II), agitation (BDI II) and restlessness (GAD-7, PHQ-9). They also reported disturbances in sleep pattern (PHQ 9, BDI II, and TSQ). However, these questions do not differentiate between hyper- and hypo-somnolence. Changes in sleep pattern may be directly attributable to pain and discomfort, rather than their psychological state per se. That said, pain can also affect psychological state and consequently affect sleep indirectly as well. This is difficult to discern, but it is likely that psychological symptoms from burns are over-represented due to a complex relationship with somatic symptoms; further research to explore this is indicated. Sleep disturbance is also pertinent to cognitive impairment as a recognised modulator of neuroplasticity and as a factor that is intrinsically associated with BICU admissions[77].

Although a statistically significant difference was found between the groups in the psychosis tool, the absolute scores were very low and the only domains that accrued points were those of depression and cognitive impairment. As such, the results were not clinically significant. No clinical evidence of psychosis or neurosis was noted in any of the participants throughout the follow up period.

4.3. Cognitive function

This study found evidence of a significant and broad cognitive deficit in the BICU patients when compared to the comparator group and to population data. We did not find any evidence of a domain specific pattern of cognitive dysfunction, thus suggesting a more global deficit spanning working memory, delayed recall, attention, executive function and language. Cognitive impairment after ICU admissions and major surgery is well described in the literature, with deficits in executive function and memory being common findings[10,15–17,78,79]. However, this is the first study to report cognitive impairment in severe burns patients who have been admitted to BICU. Furthermore, the cohort was young and the level of comorbidity was extremely low, demonstrating that the underlying mechanisms of ITU LTCI can occur in absence of premorbid cerebral disease.

The patient group performed worse than the comparators across the cognitive tests. This supports our hypothesis. However, it should be noted that due to the difference in education levels and estimated premorbid FSIQ, the statistical validity of the comparison group is called into question. I.e. one might expect a comparison group to outperform a patient group with a lower estimated premorbid IQ even in the absence of a burns injury.

If one looks beyond the comparison group, population data can be used to assess the burns patients for evidence of cognitive impairment. The estimated premorbid IQ (108) of the patient group was half a standard deviation above the population mean (100) and on the upper border of the Average category (90-110). Indeed, none of the individual patients were scored below the Average category. As such, the null hypothesis would predict that after a severe burn, patients' cognition should still be half a standard deviation above the mean. This was not reflected by the composite z-scores, which dropped by approximately 7.5 IQ points from the baseline.

Neither the ICD 10 nor DSM-V provide a definition for POCD. The commonly quoted 1995 consensus definition is in specific reference to cardiac surgery, not BICU patients[80,81]. It also specifies that a comparison to baseline performance is essential, which is methodologically implausible for accidental injuries. Due to a lack of definition, the composition of cognitive batteries used in the literature is broad and the statistical limitations of what constitutes abnormal is not standardised[81].

We used a restrictive a priori definition of cognitive impairment, as this had not been determined prior to data collection. Upon reviewing methods described in the literature, we determined that any patient scoring two standard deviations below the mean in at least two tests was the most selective definition that could be applied to our data. This allowed inclusion of all of our data, as the cognitive performance category 'Very Poor' represents an IQ of less than 70 (two standard deviations below 100). The Cogstate®-battery included population z-scores and standard deviations for comparison. According to this definition, six patients had cognitive impairment (40%) at a median interval of 2.7 years post BICU.

The pooled cognitive results for the patient group were of a parametric distribution, which reflects population data. As such, we would expect 2.5% of the test results to be more than two SDs below the mean (6.4 of 255 tests). The patients scored almost four times as many results in the Very Poor performance range than expected, which provides compelling evidence for cognitive impairment after a severe burns injury.

A significant correlation was found between cognitive impairment and our chosen marker of burns severity (rBaux score). However, age is a substantial constituent of the scoring system and is known to correlate negatively with cognitive function. When re-tested with the age element removed from the score there was no correlation between cognitive function and burns severity. This reflects the wider literature, as many papers that have reported evidence of POCD have not found a significant correlation with markers of illness severity such as the APACHE II score [66,82]. Two patients suffered transient loss of consciousness as part of the injury. This was too low to test statistically, but it was noted that they were both in the lowest performing quartile for drop in IQ.

4.4. Limitations and biases

Recruitment was adversely affected by attrition bias. Of the 40 eligible patients, 12 were not contactable and 9 declined to participate in the study. Most patients did not provide a rationale for non-participation but those recorded included: complex community care needs, mental health issues, difficulty with planning, claustrophobia and social anxiety (facial burns). Fewer than half of the eligible patients were able to participate in this study. Patients with significant mental health problems and/or known drug and alcohol misuse issues were excluded from this trial, and those with the most severe cognitive impairment were least likely to attend. We may have recruited a higher-performing subgroup with consequent under-reporting of LTCI incidence and severity. Furthermore, both the patient and the comparator groups had higher than average baseline estimated FSIQs with a significant discrepancy between the two. This calls into question the validity of the comparison and it was necessary to support the hypothesis with population data.

The BAI and BDI-II contained multiple somatic symptoms of anxiety and depression that are common sequelae of burn injuries, e.g. 'tingling in the fingers'. This resulted in uncertainty amongst the patients and possible over-reporting of psychological symptoms. Patients were instructed to respond to this

questionnaire with the understanding that each item was designed to assess the psychological and physical symptoms of anxiety. Similarly, the Neuro-QoL SF v2 appeared to have low discrimination from depression in this cohort, and this requires further investigation

5. Conclusions

In summary, patients who experienced an admission to BICU with a severe burns injury demonstrated a reduction in cognitive function when compared to both the comparator groups and to population data. Affected domains included learning and memory, attention and processing speed, executive function and language when tested against an age and sex-matched comparator group. Burns patients also have a reduction in Quality of Life, which was strongly associated with elevated symptoms of depression and post-traumatic stress. This degree of cognitive impairment reflects that of general ITU cohorts, but in a younger and low-comorbidity cohort. No correlation was found between Quality of Life and cognitive impairment. This may be due to the QoL tools used, or the high levels of depressive symptoms affecting patient perception of cognition. Further large, prospective clinical studies are required to confirm these findings.

6. Recommendations for future research

More research into long-term cognitive deficits after severe burns injury is needed to validate these cognitive findings in other populations, as well as to profile any changes with time after injury. The use of more sophisticated and ecologically valid cognitive assessments may also be useful in this clinical group to increase sensitivity and specificity across memory and executive function in order to capture cognitive impairments in everyday function. More detailed assessment would also inform our clinical and theoretical understanding of the neurocognitive impact of burns and the development of targeted cognitive rehabilitation interventions. Furthermore, validation of psychology questionnaires in burns patients is indicated to investigate and account for the large crossover of somatic symptoms in this population.

7. Acknowledgements and funding

We are grateful to all of our patients and comparator subjects for participation in this study, to the Katie Piper Foundation for helping to circulate our work for purposes of patient recruitment and to the C&W Plus charity for funding the materials and expenses for the study (reference number 556). Chelsea and Westminster Hospital provided funding for the research fellowships for AA, EJRW, MF, NAN and OHC, Westminster University funded the psychologists AM, AN and KN.

8. References

[1] Brusselaers N, Hoste EAJ, Monstrey S, Colpaert KE, De Waele JJ, Vandewoude KH, et al. Outcome and changes over time in survival following severe burns from 1985 to 2004. Intensive Care Med 2005;31:1648–53. doi:10.1007/s00134-005-2819-6.

[2] Lionelli GT, Pickus EJ, Beckum OK, DeCoursey RL, Korentager RA. A three decade analysis of factors affecting burn mortality in the elderly. Burns 2005;31:958–63. doi:10.1016/j.burns.2005.06.006.

[3] Jackson PC, Hardwicke J, Bamford A, Nightingale P, Wilson Y, Papini R, et al. Revised estimates of mortality from the Birmingham Burn Centre, 2001-2010: a continuing analysis

over 65 years. Ann Surg 2014;259:979–84. doi:10.1097/SLA.0b013e31829160ca.

[4] Cope O, Rhinelander FW. The Problem of Burn Shock Complicated by Pulmonary Damage. Ann Surg 1943;117:915–928.

[5] Beecher HK. Resuscitation and sedation of patients with burns which include the airway: Some problems of immediate therapy. Ann Surg 1943;117:825–33.

[6] Druery M, La T, Brown H, Muller M. Long term functional outcomes and quality of life following severe burn injury. Burns 2005;31:692–5. doi:10.1016/j.burns.2005.03.001.

[7] Desai S V., Law TJ, Needham DM. Long-term complications of critical care. Crit Care Med 2011;39:371–9. doi:10.1097/CCM.0b013e3181fd66e5.

[8] Goverman J, Mathews K, Nadler D, Henderson E, McMullen K, Herndon D, et al. Satisfaction with life after burn: A Burn Model System National Database Study. Burns 2016;42:1067–73. doi:10.1016/j.burns.2016.01.018.

[9] Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term Cognitive Impairment and Functional Disability Among Survivors of Severe Sepsis. Jama-Journal Am Med Assoc 2010;304:1787–94. doi:DOI 10.1001/jama.2010.1553.

[10] Girard T, Pun BT, Thompson JL, Shintani AK, Gordon SM, Canonico AE, et al. Delirium as a Predictor of Long-Term Cognitive Impairment in Survivors of Critical Illness 2013;38:1513–20. doi:10.1097/CCM.0b013e3181e47be1.Delirium.

[11] Jones C, Griffiths RD, Slater T, Benjamin KS, Wilson S. Significant cognitive dysfunction in non-delirious patients identified during and persisting following critical illness. Intensive Care Med 2006;32:923–6. doi:10.1007/s00134-006-0112-y.

[12] Ehlenbach WJ, Crane PK, Haneuse SJPA, Carson SS, Curtis JR, Larson EB. Association Between Acute Care and Critical Illness Hospitalization. JAMA 2010;303:763–70.

[13] Sukantarat KT, Burgess PW, Williamson RCN, Brett SJ. Prolonged cognitive dysfunction in survivors of critical illness. Anaesthesia 2005;60:847–53. doi:10.1111/j.1365-2044.2005.04148.x.

[14] Hough CL, Herridge MS. Long-term outcome after acute lung injury. Curr Opin Crit Care 2012;18:8–15. doi:10.1097/MCC.0b013e32834f186d.

[15] Pandharipande P, Girard TD, Jackson JC. Association between Brain Volumes, Delirium Duration and Cognitive Outcomes in Intensive Care Unit Survivors: A Prospective Exploratory Cohort Magnetic. Crit Care … 2012;40:2022–32. doi:10.1097/CCM.0b013e318250acc0.The.

[16] Duggan MC, Wang L, Wilson JE, Dittus RS, Ely EW, Jackson JC. The relationship between executive dysfunction , depression , and mental health-related quality of life in survivors of critical illness : Results from the BRAIN-ICU investigation ☆ , ☆☆. J Crit Care 2017;37:72–9. doi:10.1016/j.jcrc.2016.08.023.

[17] Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, et al. Long-Term Cognitive Impairment after Critical Illness. N Engl J Med 2013;369:1306–16. doi:10.1056/NEJMoa1301372.

[18] Wolters AE, Slooter AJC, van der Kooi AW, van Dijk D. Cognitive impairment after intensive care unit admission : a systematic review. Intensive Care Med 2013;39:376–86. doi:10.1007/s00134-012-2784-9.

[19] Li J, Bentzen SM, Li J, Renschler M, Mehta MP. Relationship Between Neurocognitive Function and Quality of Life After Whole-Brain Radiotherapy in Patients With Brain Metastasis. Int J Radiat Oncol Biol Phys 2008;71:64–70. doi:10.1016/j.ijrobp.2007.09.059.

[20] Phillips-Bute B, Mathew JP, Blumenthal J a, Grocott HP, Laskowitz DT, Jones RH, et al.

Association of neurocognitive function and quality of life 1 year after coronary artery bypass graft (CABG) surgery. Psychosom Med 2006;68:369–75. doi:10.1097/01.psy.0000221272.77984.e2.

[21] Newman MF, Grocott HP, Mathew JP, White WD, Reves JG, Laskowitz DT, et al. Report of the Substudy Assessing the Impact of Neurocognitive Function on Quality of Life 5 Years. Stroke 2001;32:2874–81. doi:10.1161/hs1201.099803.

[22] Reginold W, Duff-Canning S, Meaney C, Armstrong MJ, Fox S, Rothberg B, et al. Impact of mild cognitive impairment on health-related quality of life in Parkinson's disease. Dement Geriatr Cogn Disord 2013;36:67–75. doi:10.1159/000350032.

[23] Klepac N, Trkulja V, Relja M, Babić T. Is quality of life in non-demented Parkinson's disease patients related to cognitive performance? A clinic-based cross-sectional study. Eur J Neurol 2008;15:128–33. doi:10.1111/j.1468-1331.2007.02011.x.

[24] Teng E, Tassniyom K, Lu PH. Reduced quality-of-life ratings in mild cognitive impairment: analyses of subject and informant responses. Am J Geriatr Psychiatry 2012;20:1016–25. doi:10.1097/JGP.0b013e31826ce640.

[25] Singerman J, Gomez M, Fish JS. Long-Term Sequelae of Low-Voltage Electrical Injury: J Burn Care Res 2008;29:773–7. doi:10.1097/BCR.0b013e318184815d.

[26] Ramati A, Pliskin NH, Keedy S, Erwin RJ, Fink JW, Bodnar EN, et al. Alteration in functional brain systems after electrical injury. J Neurotrauma 2009;26:1815–22. doi:10.1089/neu.2008-0867.

[27] Ramati A, Rubin LH, Wicklund A, Pliskin NH, Ammar AN, Fink JW, et al. Psychiatric morbidity following electrical injury and its effects on cognitive functioning. Gen Hosp Psychiatry 2009;31:360–6. doi:10.1016/j.genhosppsych.2009.03.010.

[28] Aase DM, Fink JW, Lee RC, Kelley KM, Pliskin NH. Mood and cognition after electrical injury: A follow-up study. Arch Clin Neuropsychol 2014;29:125–30. doi:10.1093/arclin/act117.

[29] Wade CE, Mora AG, Shields BA, Pidcoke HF, Baer LA, Chung KK, et al. Signals from fat after injury: Plasma adipokines and ghrelin concentrations in the severely burned. Cytokine 2013;61:78–83. doi:10.1016/j.cyto.2012.08.031.

[30] Flierl MA, Stahel PF, Touban BM, Beauchamp KM, Morgan SJ, Smith WR, et al. Bench-to-bedside review: Burn-induced cerebral inflammation – a neglected entity? Crit Care 2009;13:215. doi:10.1186/cc7794.

[31] Latenser BA. Critical care of the burn patient: the first 48 hours. Crit Care Med 2009;37:2819–26. doi:10.1097/CCM.0b013e3181b3a08f.

[32] Wolf SE, Arnoldo BD. The year in burns 2011. Burns 2012;38:1096–108. doi:10.1016/j.burns.2012.10.002.

[33] Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, et al. Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study. Lancet 1998;351:857–61. doi:10.1016/S0140-6736(97)07382-0.

[34] Bekker AY, Weeks EJ. Cognitive function after anaesthesia in the elderly. Best Pract Res Clin Anaesthesiol 2003;17:259–72. doi:10.1016/S1521-6896(03)00005-3.

[35] Monk G, Weldon Craig B, Garvan W, Dede E, van Maria T, Heilman M, et al. Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology 2008;108:18. doi:10.1097/01.anes.0000296071.19434.1e.

[36] Steinmetz J, Christensen KB, Lund T, Lohse N, Rasmussen LS. Long-term Consequences of Postoperative Cognitive Dysfunction. Anesthesiology 2009;110:548–55.

doi:10.1097/ALN.0b013e318195b569.

[37] Mason SE, Noel-Storr A, Ritchie CW. The impact of general and regional anesthesia on the incidence of post-operative cognitive dysfunction and post-operative delirium: a systematic review with meta-analysis. J Alzheimers Dis 2010;22 Suppl 3:67–79. doi:10.3233/JAD-2010-101086.

[38] Schultzberg M, Lindberg C, Aronsson ÅF, Hjorth E, Spulber SD, Oprica M. Inflammation in the nervous system - Physiological and pathophysiological aspects. Physiol Behav 2007;92:121–8. doi:10.1016/j.physbeh.2007.05.050.

[39] Fung A, Vizcaychipi M, Lloyd D, Wan Y, Ma D. Central nervous system inflammation in disease related conditions: Mechanistic prospects. Brain Res 2012;1446:144–55. doi:10.1016/j.brainres.2012.01.061.

[40] Banks WA, Ortiz L, Plotkin SR, Kastin a J. Human interleukin (IL) 1 alpha, murine IL-1 alpha and murine IL-1 beta are transported from blood to brain in the mouse by a shared saturable mechanism. J Pharmacol Exp Ther 1991;259:988–96.

[41] Pan W, Kastin AJ. TNFalpha transport across the blood-brain barrier is abolished in receptor knockout mice. Exp Neurol 2002;174:193–200. doi:10.1006/exnr.2002.7871.

[42] Goehler LE, Gaykema RPA, Opitz N, Reddaway R, Badr N, Lyte M. Activation in vagal afferents and central autonomic pathways: Early responses to intestinal infection with Campylobacter jejuni. Brain Behav Immun 2005;19:334–44. doi:10.1016/j.bbi.2004.09.002.

[43] Kohman RA, Rhodes JS. Neurogenesis, inflammation and behavior. Brain Behav Immun 2013;27:22–32. doi:10.1016/j.bbi.2012.09.003.

[44] Wunder A, Klohs J, Dirnagl U. Non-invasive visualization of CNS inflammation with nuclear and optical imaging. Neuroscience 2009;158:1161–73. doi:10.1016/j.neuroscience.2008.10.005.

[45] Jacobs AH, Tavitian B, Consortium I. Noninvasive molecular imaging of neuroinflammation. J Cereb Blood Flow Metab 2012;32:1393–415. doi:10.1038/jcbfm.2012.53.

[46] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 1987;40:373–83. doi:10.1016/0021-9681(87)90171-8.

[47] Osler T, Glance LG, Hosmer DW. Simplified estimates of the probability of death after burn injuries: Extending and updating the baux score. J Trauma - Inj Infect Crit Care 2010;68:690–7. doi:10.1097/TA.0b013e3181c453b3.

[48] Spitzer RL, Kroenke K, Williams JBW. Validation and Utility of a Self-report Version of PRIME-MD. JAMA J Am Med Assoc 1999;282:1737–44. doi:10.1001/jama.282.18.1737.

[49] Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: Validity of a brief depression severity measure. J Gen Intern Med 2001;16:606–13. doi:10.1046/j.1525-1497.2001.016009606.x.

[50] Beck A, Ward C, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–71.

[51] Beck AT, Steer RA, Carbin MG. Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. Clin Psychol Rev 1988;8:77–100. doi:10.1016/0272-7358(88)90050-5.

[52] Brewin CR, Rose S, Andrews B, Green J, Tata P, McEvedy C, et al. Brief screening instrument for post-traumatic stress disorder. Br J Psychiatry 2002;181:158–62. doi:10.1192/bjp.181.2.158.

[53] Dekkers AMM, Olff M, Maring GWB. Identifying persons at risk for PTSD after trauma with

TSQ in the Netherlands. Community Ment Health J 2010;46:20–5. doi:10.1007/s10597-009-9195-6.

[54] Löwe B, Decker O, Müller S, Brähler E, Schellberg D, Herzog W, et al. Validation and standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the general population. Med Care 2008;46:266–74. doi:10.1097/MLR.0b013e318160d093.

[55] Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 1988;56:893–7. doi:10.1037/0022-006X.56.6.893.

[56] Fydrich T, Dowdall D, Chambless DL. Reliability and validity of the beck anxiety inventory. J Anxiety Disord 1992;6:55–61. doi:10.1016/0887-6185(92)90026-4.

[57] Maruff P, Thomas E, Cysique L, Brew B, Collie A, Snyder P, et al. Validity of the CogState brief battery: Relationship to standardized tests and sensitivity to cognitive impairment in mild traumatic brain injury, schizophrenia, and AIDS dementia complex. Arch Clin Neuropsychol 2009;24:165–78. doi:10.1093/arclin/acp010.

[58] Nelson H, Willison J. National Adult Reading Test (NART). 2nd ed. NFER-NELSON Publishing Company Ltd; 1991.

[59] Nelson HE, McKenna P. The Use of Current Reading Ability in the Assessment of Dementia. Br J Soc Clin Psychol 1975;14:259–67.

[60] Morrison G, Sharkey V, Allardyce J, Kelly R, McCreadie R. Nithsdale schizophrenia surveys 21: a longitudinal study of National Adult Reading Test stability. Psychol Med 2000;30:717–20.

[61] Smith D, Roberts S, Brewer W, Pantelis C. Test-retest Reliability of the National Adult Reading Test (NART) as an Estimate of Premorbid IQ in Patients with Schizophrenia. Cogn Neuropsychiatry 1998;3:71–80. doi:10.1080/135468098396251.

[62] KJ W, RE O. Evaluating methods for estimating premorbid intellectual ability in closed head injury. J Neurol Neurosurg Psychiatry 1999;66:474–9.

[63] Persson J, Pudas S, Lind J, Kauppi K, Nilsson LG, Nyberg L. Longitudinal structure-function correlates in elderly reveal MTL dysfunction with cognitive decline. Cereb Cortex 2012;22:2297–304. doi:10.1093/cercor/bhr306.

[64] Parra M a, Pattan V, Wong D, Beaglehole A, Lonie J, Wan HI, et al. Medial temporal lobe function during emotional memory in early Alzheimer's disease, mild cognitive impairment and healthy ageing: an fMRI study. BMC Psychiatry 2013;13:76. doi:10.1186/1471-244X-13-76.

[65] McPhail MJ, Leech R, Grover VP, Fitzpatrick JA, Dhanjal NS, Crossey MM, et al. Modulation of neural activation following treatment of hepatic encephalopathy. Neurology 2013;80:1041–7. doi:10.1212/WNL.0b013e31828726e1\rWNL.0b013e31828726e1 [pii].

[66] Hopkins RO, Weaver LK, Collingridge D, Parkinson RB, Chan KJ, Orme JF. Two-Year Cognitive, Emotional, and Quality-of-Life Outcomes in Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 2005;171:340–7. doi:10.1164/rccm.200406-763OC.

[67] Pugsley W, Klinger L, Paschalis C, Treasure T, Harrison M, Newman S. The impact of microemboli during cardiopulmonary bypass on neuropsychological functioning. Stroke 1994;25:1393–9. doi:10.1161/01.STR.25.7.1393.

[68] Patel RL, Turtle MR, Chambers DJ, James DN, Newman S, Venn GE. Improves Neuropsychologic Outcome in Patients Undergoing Coronary. J Thorac Cardiovasc Surg 1996;111:1267–79.

[69] Lim WC, Black N, Lamping D, Rowan K, Mays N. Conceptualizing and measuring health-related quality of life in critical care. J Crit Care 2016;31:183–193.

doi:10.1016/j.jcrc.2015.10.020.

[70] Ankri J, Beaufils B, Novella JL, Morrone I, Guillemin F, Jolly D, et al. Use of the EQ-5D among patients suffering from dementia. J Clin Epidemiol 2003;56:1055–63. doi:10.1016/S0895-4356(03)00175-6.

[71] Newman S, Klinger L, Venn G, Smith P, Harrison M, Treasure T. Subjective reports of cognition in relation to assessed cognitive performance following coronary artery bypass surgery. J Psychosom Res 1989;33:227–33.

[72] Logsetty S, Shamlou A, Gawaziuk JP, March J, Doupe M, Chateau D, et al. Mental health outcomes of burn: A longitudinal population-based study of adults hospitalized for burns. Burns 2016;42:738–44. doi:10.1016/j.burns.2016.03.006.

[73] Ward HW, Moss RL, Darko DF, Berry CC, Anderson J, Kolman P, et al. Prevalence of postburn depression following burn injury. J Burn Care Rehabil 1987;8:294–8.

[74] Ehde DM, Patterson DR, Wiechman SA, Wilson LG. Post-traumatic stress symptoms and distress 1 year after burn injury. J Burn Care Rehabil 2000;21:105–11. doi:10.1097/00004630-200021020-00005.

[75] Wiechman S a, Ptacek JT, Patterson DR, Gibran NS, Engrav LE, Heimbach DM. Rates, trends, and severity of depression after burn injuries. J Burn Care Rehabil 2001;22:417–24. doi:10.1097/00004630-200111000-00012.

[76] Pavoni V, Gianesello L, Paparella L, Buoninsegni LT, Barboni E. Outcome predictors and quality of life of severe burn patients admitted to intensive care unit. Scand J Trauma Resusc Emerg Med 2010;18:24. doi:10.1186/1757-7241-18-24.

[77] Yang G, Sau C, Lai W, Cichon J, Li W. Sleep promotes branch-specific formation of dendritic spines after learning. Science (80-) 2015;344:1173–8. doi:10.1126/science.1249098.Sleep.

[78] Zhao J, Wang C, Sun Y, Sun Z. The effects of cognitive intervention on cognitive impairments after intensive care unit admission. Neuropsychol Rehabil 2017;27:301–17. doi:10.1080/09602011.2015.1078246.

[79] Hopkins RO, Brett S. Chronic neurocognitive effects of critical illness. Curr Opin Crit Care 2005;11:369–75. doi:10.1097/01.ccx.0000166399.88635.a5.

[80] Murkin JM, Newman SP, Stump DA, Blumenthal JA. Statement of Consensus on Assessment of Neurobehavioral Outcomes After Cardiac Surgery. Ann Thorac Surg 1995;59:1289–95.

[81] Rasmussen L, Larsen K, Houx P, Skovgaard L, Hanning C, Moller J, et al. The International Study of Postoperative Cognitive Dysfunction. The assessment of postoperative cognitive function. Acta Anaesthesiol Scand 2001;45:275–89.

[82] Jackson J, Gordon S, Burger C, Ely E, Thomason J, Hopkins R. Acute respiratory distress syndrome and long-term cognitive impairment: a case study. Arch Clin Neuropsychol 2003;18:688.

[83] Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332. doi:https://doi.org/10.1136/bmj.c332.