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The relationship between pain, anxiety and depression in patients with post-intensive care syndrome

Christie Docherty [a,*], Joanne McPeake [b], Tara Quasim [a,c], Pamela MacTavish [c], Helen Devine [d], Peter O'Brien [d], Laura Strachan [e], Phil Lucie [f], Lucy Hogg [g], Malcolm Sim [a,e], Martin Shaw [a,h]

[a] School of Medicine, Dentistry and Nursing, University of Glasgow, Glasgow, UK
[b] The Healthcare Improvement Studies Institute, University of Cambridge, Cambridge, UK
[c] Intensive Care Unit, Glasgow Royal Infirmary, Glasgow, UK
[d] Intensive Care Unit, University Hospital Crosshouse, Kilmarnock, UK
[e] Intensive Care Unit, Queen Elizabeth University Hospital, Glasgow, UK
[f] Intensive Care Unit, University Hospital Wishaw, North Lanarkshire, UK
[g] Intensive Care Unit, Victoria Hospital, Kirkcaldy, UK
[h] Clinical Physics, NHS Greater Glasgow and Clyde, Glasgow, UK

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ABSTRACT

Purpose: Survivors of critical illness frequently experience long-term symptoms including physical symptoms such as pain and emotional symptoms such as anxiety and depression. These symptoms frequently co-exist, however, at present there is limited understanding of these relationships. The aim of this study was to quantify the relationship between pain, anxiety and depression across the recovery trajectory.

Methods: This study is a secondary analysis of data from a multi-centre, prospective, cohort study which followed-up patients recovering from critical illness. Data was available at multiple time points and for 3 distinct cohorts. Structural equation modelling was used to investigate the relationship between outcome measures of pain, anxiety and depression.

Results: Data from 414 patients was analysed. Pain was significantly associated with both anxiety and depression in all cohorts and at all time points sampled. Path coefficients for the covariances between pain and depression ranged between 0.39 and 0.72 ($p < 0.01$). Path coefficients for the covariances between pain and anxiety ranged between 0.39 and 0.65 ($p < 0.01$).

Conclusions: Pain, anxiety and depression are highly correlated in survivors of critical illness. Pharmacological treatments for pain management may be ineffective alone and further research is required to assess interventions targeting these symptoms in combination.

1. Introduction

Post-Intensive Care Syndrome (PICS) describes the long-term impairments and symptoms seen in survivors of critical illness [1]. PICS symptoms are classically divided into 3 component domains: physical; cognitive and emotional symptoms [2]. Symptoms or impairments spanning multiple domains frequently co-exist, with survivors of critical illness reporting symptoms across multiple domains up to one year post-discharge [3].

Pain is one of the most frequently reported symptoms in the physical domain of PICS, affecting up to 66% of survivors of critical illness [4-6]. In chronic pain of other aetiologies, it has been well documented that there is significant co-prevalence of chronic pain and mental health conditions such as depression and Post Traumatic Stress Disorder

Abbreviations: PICS, Post-Intensive Care Syndrome.

* Corresponding author at: Academic Unit of Anaesthesia, Critical Care and Peri-Operative Medicine, Floor 2, New Lister Building, Glasgow Royal Infirmary, 10-16 Alexandra Parade, Glasgow, G31 2ER, UK.

E-mail addresses: christie.docherty@glasgow.ac.uk (C. Docherty), joanne.mcpeake@glasgow.ac.uk (J. McPeake), tara.quasim@glasgow.ac.uk (T. Quasim), pamela.mactavish@ggc.scot.nhs.uk (P. MacTavish), helen.devine4@aapct.scot.nhs.uk (H. Devine), peter.o'brien@aapct.scot.nhs.uk (P. O'Brien), laura.strachan@ggc.scot.nhs.uk (L. Strachan), phil.lucie@lanarkshire.scot.nhs.uk (P. Lucie), lucy.hogg1@nhs.scot (L. Hogg), malcolm.sim@glasgow.ac.uk (M. Sim), martin.shaw@ggc.scot.nhs.uk (M. Shaw).

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(PTSD) [7,8]. Moreover, in patients with chronic pain, emotional distress has been shown to be associated with increased severity of pain, increased disability and poorer treatment response [9,10].

Patients with PICS, are however, notable for their heterogeneity and multimorbidity. These patients were admitted to intensive care with a variety of different primary pathologies and progressed differently during their critical illness. During the recovery phase, they also present very heterogeneously, with different clusters of symptoms and varying severity. The relationships between symptoms seen in other cohorts of patients may not therefore be reflected in patients with PICS. Although, it is known that the development of critical illness related pain contributes to disability and impacts on patients' quality of life [5,11], at present the association between pain and emotional symptoms in survivors of critical illness remains unknown. An improved understanding of this relationship would help to establish which patients are at high risk for these symptoms, to ensure that screening is implemented where appropriate and to refine treatment.

Therefore, the aim of this study was to quantify the relationship between pain, anxiety and depression across the recovery trajectory.

2. Methods

2.1. Study design

This study is a secondary analysis of data collected as part of a multicentre, prospective cohort study evaluating the impact of an ICU recovery programme. The InS:PIRE programme (Intensive care Syndrome: Promoting Independence and Return to Employment) is a health and social care intervention, delivered by a multi-disciplinary team including doctors, nurses, pharmacists, physiotherapists and clinical neuropsychologists. Support from peers and local community organisations are embedded into the sessions. Full details of the programme have been published elsewhere [12,13].

We report on data from 3 separate cohorts: The intervention cohort; the usual care cohort and the COVID-19 cohort. Full details of all cohorts have been published elsewhere [14,15]. Patients in the intervention and COVID-19 cohorts were recruited from the InS:PIRE programme, while those in the usual care cohort had been admitted to ICU but did not undergo the follow up intervention. The decision was taken to report on these 3 cohorts separately as longitudinal data was only available for one cohort and the sampling was at different time points in the other two cohorts (as described below). Moreover, by reporting on these cohorts separately it ensures that differences or similarities between the groups may be seen.

The intervention cohort was recruited between May 2016 and May 2018 from five hospitals in Scotland. Data was recorded from this cohort of patients at three time points: baseline, immediately prior to commencing the InS:PIRE intervention (between 1 and 3 months following hospital discharge); 3 months post-intervention; and 12 months post-intervention.

The usual care cohort were recruited between June 2017 and March 2020 from eight hospitals in Scotland. This cohort of patients were recruited 10 to 16 months following hospital discharge via postal survey. Data was available for the usual care cohort at this single time point.

Patients in the COVID-19 cohort had been admitted to critical care between March 2020 and May 2020 with either confirmed or a high clinical suspicion of Sars-CoV-2 infection. Data collection was completed by telephone or postal questionnaire. Data is available for this cohort at a single time point, 3–7 months post hospital discharge, at their initial InS:PIRE appointment.

Patients were asked to complete the following questionnaires at each of the various time points: EQ-5D-5L [16]; Brief Pain Inventory [17]; Hospital Anxiety and Depression Score [18]. These tools are commonly employed to assess PICS symptoms in survivors of critical illness [19,20]. Further details of these tools are available in Supplemental 1.

2.2. Inclusion criteria

The following patients were eligible for enrolment in the InS:PIRE programme: Patients receiving level 3 care [21] (multiple organ support and/or invasive respiratory support); Patients receiving more than seven days of level 2 care [21] (single organ support or postoperative care); Patients deemed by clinicians to be at high risk of post-intensive care syndrome taking into account known risk factors such as mental health comorbidity, severity of illness, negative ICU experience and delirium [22]. Exclusion criteria were as follows: any patient who was terminally ill; any patient who had suffered a traumatic brain injury; patients who remained an in-patient under psychiatric services; any patient currently incarcerated in prison. These inclusion and exclusion criteria were consistent across all 3 cohorts with the additional criteria that patients recruited to the COVID-19 cohort had been admitted to ICU with confirmed or a high clinical suspicion of SARS-CoV-2 infection.

2.3. Data analysis

2.3.1. Structural equation modelling

Structural equation modelling (SEM) is a technique which is used to define and model complex relationships between variables. This method was chosen as it can accurately model the relationships between pain, anxiety and depression in survivors of critical illness, while minimising measurement error and accounting for multiple testing within the model.

When creating a SEM, a hypothetical model is first constructed based on theoretical understanding of the likely relationships between variables. SEM combines elements of a variety of statistical techniques including confirmatory factor analysis and path analysis to determine to what extent the hypothesised relationships are reflected in the observed data [23]. This model can then be further refined. An advantage of SEM is that it accounts for multiple testing within the model matrix and can minimise measurement error associated with the use of single fixed variables [24].

SEM allows for relationships between abstract concepts to be analysed. These abstract concepts are termed latent variables and cannot be directly measured e.g., pain. Instead, they are identified and estimated using a variety of observed variables within the dataset e.g., Questionnaire responses [25]. Standard notation dictates that latent variables are represented by ovals in the path diagram and observed variables are represented by rectangles. Single headed arrows confer directionality of a relationship, whereas double headed arrows confer covariance [25]. The path coefficient indicates the strength of the relationship between the two variables. The path coefficient is a standardised regression coefficient quantifying the effect of one variable on another [26].

The goodness of fit of the observed data to the hypothesised model is evaluated statistically. A variety of fit measures are available; we selected 3 for use in this study. First, we assessed the comparative fit index (CFI). This compares the chi-squared value of the model to the chi-squared value of the null model [27]. Accepted criteria suggests that CFI should be >0.90. Second, we assessed the Standardised Root Mean Residual (SRMR). This evaluates the difference between the residuals of the sample covariance matrix and the hypothesised covariance model [27]. The SRMR should be <0.08 to indicate a good fit. Thirdly we assessed the Root Mean Square Error of Approximation (RMSEA). This is an absolute measure of fit, accounting for sample size. It tells us how well the model with unknown, but optimally chosen parameters would fit the population covariance network [27]. Accepted criteria suggests that for a good fit this should be <0.06 [24]. The use of SEM was appropriate for this study as our data set contained multiple measurement points estimating each latent variable. In addition, this technique allows the flexibility to create expanded or truncated models for the various cohorts analysed in this study [28]. Identification and evaluation of the hypothesised model was performed using the Lavaan software package [29].

2.3.2. The hypothesised model

The hypothesised model was developed based on a combination of evidence from other clinical fields, clinical experience and treating patients experiencing of PICS within the InS:PIRE programme [30-32]. It was hypothesised that pain correlates with both symptoms of anxiety and depression in survivors of critical illness. A bidirectional relationship was specified as it was hypothesised that pain would contribute to patients' feelings of anxiety and depression and that anxiety and depression would also impact the patient's experience of pain (as, for example. They may be more likely to ruminate on it).

Data was available for the Usual Care and COVID-19 cohorts at a single time point, therefore, a truncated model was created to analyse the relationships between these variables. This model is displayed in the path diagram in Fig. 1.

For the Intervention cohort it was hypothesised that the correlation between pain and each of anxiety and depression would remain true each of the timepoints included. In addition, it was hypothesised that pain at baseline would predict pain at 3 months, which would in turn predict pain at 12 months. This expanded model is displayed in a path diagram in Fig. 2.

2.3.3. Model refinement

In order to evaluate whether bidirectional relationships between pain anxiety and depression or unidirectional relationships, where anxiety and depression predict pain, were best reflected in the observed data, models specifying unidirectional relationships were also ran. These results are available in Supplemental 2.

2.3.4. Latent variable identification

The pain latent variable was constructed as a composite of the following 3 observed variables: the patient's response to the single pain and discomfort question included in the EQ-5D-5L [33]; the pain severity score of the Brief Pain Inventory (mean of questions 3–6 as per creator's instructions) [34] and the pain interference score of the Brief Pain Inventory (mean of questions 9a-9g as per creator's instructions) [34].

The anxiety latent variable was predicted by each of the 7 questions relating to anxiety in the Hospital Anxiety and Depression Score.

The depression latent variable was predicted by each of the 7 questions relating to depression in the Hospital Anxiety and Depression Score.

2.3.5. Missing data

Missing data was imputed in order to reduce bias and ensure maximum power. Imputation was performed using predictive mean matching with the Multivariate Imputation by Chained Equations (MICE) software package [35]. The amount of missing data is detailed in Supplemental 3.

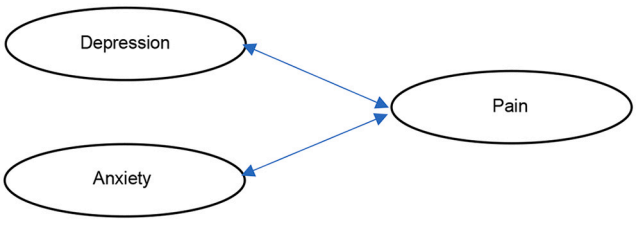

Fig. 1. Path diagram displaying the hypothesised model for the Usual care and COVID-19 cohorts.
Observed variables not displayed.

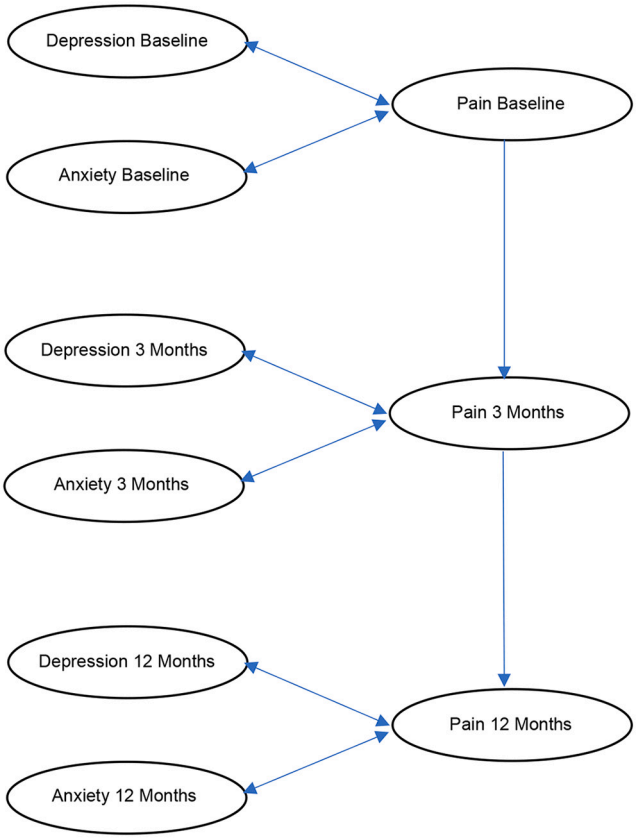

Fig. 2. Path diagram displaying the hypothesised model for the Intervention cohort.
Observed variables not displayed.

3. Results

3.1. Participants

3.1.1. Intervention cohort

During the recruitment period 570 patients were eligible to attend InS:PIRE. 253 attended and were approached to participate in the study. 206 patients consented to participate in the study. 112 (54.6%) patients were male and the median age was 58.2 (IQR: 50–65.7). Six patients died before 1-year follow-up and 63 were lost to follow-up during the duration of the study. At 3 months 141 patients remained in the study and at 12 months 137 patients remained in the study.

3.1.2. Usual care cohort

643 patients were admitted to participating ICUs during the recruitment period. After screening 452 were eligible for inclusion and sent postal packs and questionnaires. 115 (25.4%) of the patients approached responded. 67 (58.3%) of patients were male and the median age was 63.5 (IQR: 49.5–71.5).

3.1.3. COVID-19 cohort

During the recruitment period a total of 198 patients who were admitted to critical care with either confirmed, or high clinical suspicion of SARS-CoV-2 infection were eligible to attend the InS:PIRE clinic. Of those, 122 patients attended the clinic and all of those patients were invited to participate in the study. 93 patients consented to participation; 61 (65.6%) patients were male and the median age was 59 (IQR: 54–67). Patient demographics for all cohorts are displayed in Table 1.

Table 1
Patient demographics.

Characteristic	Intervention Cohort (n = 206)	Usual Care Cohort (n = 115)	COVID-19 Cohort (n = 93)	*P* Value
Age (years), median (IQR)	58 (50–66)	63 (50–71)	59 (54–67)	0.016
Gender, Male (%)	112 (54%)	66 (57%)	61 (66%)	0.12
APACHE II Score, median (IQR)	20 (15–25)	19 (14–25)	15 (12–19)	<0.001
Advanced Respiratory Support (%)	180 (87%)	100 (87%)	79 (85%)	0.3
Cardiovascular Support (%)	165 (80%)	86 (75%)	35 (38%)	<0.001
Renal Replacement Therapy (%)	43 (21%)	19 (17%)	18 (19%)	0.4
Critical Care LOS, median (IQR)	11 (6–18)	5 (2–10)	11 (5–25)	<0.001
Hospital LOS, median (IQR)	30 (16–48)	18 (12–35)	20 (12–42)	<0.001
Comorbidities				
Hypertension (%)	70 (34%)	39 (34%)	36 (39%)	0.085
Respiratory disease (%)	66 (32%)	35 (30%)	28 (30%)	0.9
Cardiovascular disease (%)	33 (16%)	22 (19%)	11 (12%)	0.5
Endocrine (%)	23 (11%)	22 (19%)	23 (25%)	0.014
Liver (%)	13 (6%)	4 (4%)	1 (1%)	0.031
Gastrointestinal (%)	45 (22%)	23 (20%)	12 (13%)	0.2
Mental Health (%)	68 (33%)	28 (24%)	12 (13%)	0.001
Socioeconomic status (SIMD quintile)				
1 (most deprived)	83 (41%)	34 (30%)	29 (32%)	
2	50 (24%)	27 (23%)	19 (21%)	
3	31 (15%)	12 (10%)	20 (22%)	
4	22 (11%)	18 (16%)	8 (9%)	
5 (least deprived)	19 (9%)	21 (18%)	16 (17%)	

3.2. Pain

The median BPI pain severity score at baseline for the intervention and COVID-19 cohorts were 4.13 (IQR: 2.00–6.00) and 2.50 (IQR: 0.00–5.25), respectively. The median BPI pain severity score at 3 months for the intervention cohort was 4.25 (IQR: 1.75–6.25). The median BPI pain severity score at 12 months for the intervention and usual care cohorts were 3.50 (IQR: 1.50–5.00) and 3.25 (IQR: 0.88–5.63), respectively.

The median BPI pain interference score at baseline for the intervention and COVID-19 cohorts were 4.54 (IQR: 1.61–7.29) and 1.86 (IQR: 0.00–6.29), respectively. The median BPI pain interference score at 3 months for the intervention cohort was 3.93 (IQR: 1.68–7.14). The median BPI pain interference score at 12 months for the intervention and usual care cohorts were 3.39 (IQR: 1.00–5.54) and 2.71 (IQR: 0.36–6.86), respectively.

3.3. Depression

The median HADS depression component score at baseline for the intervention and COVID-19 cohorts were 7.00 (IQR 4.00–11.00) and 6.00 (IQR: 3.00–10.00), respectively. The median HADS depression component score at 3 months for the intervention cohort was 4.00 (IQR: 2.00–9.00). The median HADS depression component score at 12 months for the intervention and usual care cohorts were 3.00 (IQR: 0.00–7.00) and 6.00 (IQR: 2.00–11.00), respectively.

3.4. Anxiety

The median HADS anxiety component score at baseline for the intervention and COVID-19 cohorts were 8.50 (IQR: 4.00–13.00) and 6.00 (IQR: 3.00–12.00), respectively. The median HADS anxiety component score at 3 months for the intervention cohort was 6.00 (IQR: 4.00–10.50). The median HADS anxiety component score at 12 months for the intervention and usual care cohorts were 4.00 (IQR: 1.00–9.00) and 7.00 (IQR: 4.00–12.00), respectively.

3.5. Model fit

For the Intervention model the CFI was 0.909, the SRMR was 0.062 and the RMSEA was 0.034. For the Usual care model the CFI was 0.944, the SRMR was 0.56 and the RMSEA was 0.059. For the COVID-19 model the CFI was 0.945, the SRMR was 0.062 and the RMSEA was 0.057. This is suggestive of a good fit between the hypothesised model and the observed data for all models. Fit statistics are displayed in Table 2.

The fit statistics for the models specifying a unidirectional relationship, where anxiety and depression predict pain are displayed in Supplemental 2. These statistics were weaker, suggesting that the data supported bidirectional relationships. As such we continued to use the models specifying bidirectional relationships.

3.6. Relationship between pain and depression

Standardised results are quoted to ensure ease of understanding over the different scales measured by the observed variables. The path coefficients for the covariance between pain and depression at baseline for the intervention and COVID-19 cohorts were 0.66 ($p < 0.01$) and 0.69 ($p < 0.01$) respectively. The path coefficient for the covariance between pain and depression at 3 months for the intervention cohort was 0.39 ($p < 0.01$). The path coefficient for the covariance between pain and depression at 12 months for the intervention and usual care cohorts were 0.50 ($p < 0.01$) and 0.72 ($p < 0.01$) respectively.

3.7. Relationship between pain and anxiety

The path coefficients for the covariance between pain and anxiety at baseline for the intervention and COVID-19 cohorts were 0.59 ($p < 0.01$) and 0.65 ($p < 0.01$) respectively. The path coefficient for the covariance between pain and anxiety at 3 months for the intervention cohort was 0.39 ($p < 0.01$). The path coefficient for the covariance between pain and anxiety at 12 months for the intervention and usual care cohorts were 0.52 ($p < 0.01$) and 0.55 ($p < 0.01$) respectively.

3.8. Relationship between depression and anxiety

The path coefficients for the covariance between depression and anxiety at baseline for the intervention and COVID-19 cohorts were 0.85 ($p < 0.01$) and 0.91 ($p < 0.01$) respectively. The path coefficient for the covariance between depression and anxiety at 3 months for the intervention cohort was 0.88 ($p < 0.01$). The path coefficient for the covariance between depression and anxiety at 12 months for the intervention and usual care cohorts were 0.90 ($p < 0.01$) and 0.83 ($p < 0.01$) respectively.

Path coefficients between variables are displayed in Table 3.

Table 2
Fit statistics.

Cohort	CFI	SRMR	RMSEA
Intervention	0.909	0.062	0.034
Usual Care	0.944	0.056	0.059
COVID-19	0.945	0.062	0.057

Table 3
The covariances between pain, anxiety and depression.

	Pain vs Depression		Pain vs Anxiety		Depression vs Anxiety	
	Path Coefficient	P	Path Coefficient	P	Path Coefficient	P
COVID-19 Cohort 0 months	0.69	<0.01	0.65	<0.01	0.91	<0.01
Intervention Cohort 0 months	0.66	<0.01	0.59	<0.01	0.85	<0.01
Intervention Cohort 3 Months	0.39	<0.01	0.39	<0.01	0.88	<0.01
Intervention Cohort 12 Months	0.50	<0.01	0.52	<0.01	0.90	<0.01
Usual Care Cohort 12 Months	0.72	<0.01	0.55	<0.01	0.83	<0.01

3.9. Relationship between pain across various time points

As described above, data at multiple time points was only available for the Intervention cohort. For this model we were able to assess the relationship between pain at the various time points. The regression co-efficient for the relationship between pain at 3 months and pain at baseline was 0.74 ($p < 0.01$). The regression co-efficient for the relationship between pain at 12 months and pain at 3 months was 0.75 ($p < 0.01$).

4. Discussion

This study aimed to establish the relationship between pain and the emotional symptoms of PICS. This secondary analysis of prospectively collected data, has demonstrated across multiple time points that there are statistically and clinically significant correlations between pain and anxiety and depression. Clinicians should consider screening for the co-existance of these symptoms where one of them is identified as a concern. Moreover, this highlights the need for clinicians and researchers to implement multi-faceted interventions which combat this symptom cluster, rather than interventions which are focussed on isolated symptoms. Further research is required to assess the efficacy of such interventions in the post critical illness population.

The findings of this study are consistent with research in chronic pain of other aetiologies which has shown a correlation between emotional symptoms, pain severity and pain associated disability [32,36,37]. This study demonstrates a bidirectional relationship between pain and emotional symptoms. It has been suggested that emotional distress may occur as a consequence of chronic pain, but additionally, that depression may impact central pain processing and alter the patient's experience of pain [38,39]. In the critical care population, previous studies have demonstrated a correlation between pain and anxiety while patients are admitted to critical care [40]. In addition, the patient's memory of pain while in ICU may predict symptoms of psychological distress at one year [41]. However, to our knowledge no other studies have quantified this relationship throughout the recovery trajectory in survivors of critical illness.

The results of this study are not only statistically significant, but also clinically significant. Across the different cohorts at the various time points sampled the association between pain and depression ranged between 39 and 72% and the association between pain and anxiety ranged between 39 and 65%. Such large associations would suggest that screening for the co-existance of these symptoms where one of them is identified as a concern would be beneficial and high yield. In the intervention cohort, we see that at 3 months post-intervention pain is less strongly associated with anxiety and depression than it was at baseline, followed by a slight increase again in the strength of these associations at 12 months. This may be partially attributable to the initial effects of the intervention. Neuropsychological input is embedded in each session of the intervention, as such it is hoped that patients may learn techniques to better manage their emotional symptoms. Perhaps at 12 months there may be a drop off in patients using these techniques and so we see a slight increase in the strength of the association between pain and emotional symptoms. As the cohorts were not matched, drawing comparisons between the cohorts was not possible.

In chronic pain research it has been well-established that analgesia alone is often insufficient to manage patients symptoms [42]. In addition, there is concern that failing to address the other factors contributing to the patient's experience of chronic pain could contribute to increasing analgesic requirements, including opiate use [43,44]. A multi-disciplinary approach to pain management has been advocated [45,46] and there is a strong body of evidence supporting the use of psychological therapies to manage chronic pain of other aetiologies [47]. However, at present there has been limited study of the efficacy of therapeutic interventions to manage pain specifically in the post-critical illness population [48]. We propose that patients experiencing chronic pain following critical illness may benefit from a similar treatment programme, incorporating input from pain specialists, physiotherapists and psychologists. Further research should prioritise evaluating the effectiveness of such an intervention in survivors of critical illness.

This study demonstrates a strong relationship between pain, anxiety and depression for all cohorts, including a cohort of patients admitted to ICU with SARS-CoV-2 infection. It is established that social isolation, necessitated by the pandemic, resulted in a significant impact on the mental health of the community in general [49,50]. However, the effect of isolation was seen to be more pronounced in those with chronic illness [51], who may be more reliant on external support.

The key strengths of this study are that it utilises data from prospective, multicentre studies comprised of three groups with diverse baseline characteristics. The underlying relationships between pain and the psycho-social symptoms of PICS remain true across the different cohorts included which would suggest external validity of these concepts. The ability to draw data from a large number of observed variables, used to estimate each of the latent variables across the included models, also enhances the accuracy of estimation.

However, there are limitations to this work, for example, data was only available across multiple time points for one of the three cohorts described. The patient numbers in this cohort limited the power of the data and as such that it was not able to support more complex models evaluating the longitudinal paths of all 3 of pain, anxiety and depression. In addition, the change in pain scores over time for this cohort could be at least partially attributable to the effect of the intervention which all of the patients included in this aspect of the analysis underwent. Moreover, cohorts were not propensity matched, limiting the comparison of these relationships across the cohorts. Limited data was available for other PICS symptoms and domains such as cognitive impairment or physical impairment, which also may have important relationships with pain and would have allowed for a greater understanding of how the different domains of PICS interact.

5. Conclusions

Pain, anxiety and depression are all highly correlated in survivors of critical illness. Pharmacological treatments for pain management may be ineffective alone and further research is required to assess interventions targeting these symptoms in combination.

Ethics approval details

Ethical approval was granted by the Liverpool Central Research Ethics Committee (reference: 17/NM/0199). All participants provided written consent.

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Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Author statements

MS, CD and JM conceptualised the study. PH, JM, MS and TQ acquired the data. CD, MS and JM were responsible for data analysis and interpretation. CD authored the first draft of the paper. All authors were involved in revising the manuscript and have given final approval of this version.

Declaration of Competing Interest

There are no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2023.154359.

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