Review Article

Association between inflammation and post-intensive care syndrome: a systematic review

C. Docherty,[1] **C. Page,**[2] **J. Wilson,**[3] **P. Ross,**[4] **K. Garrity,**[1] **T. Quasim,**[5,6] **M. Shaw**[7,8] and **J. McPeake**[9]

1 Clinical Research Fellow, 5 Professor, 7 Honorary Senior Lecturer, Academic Unit of Anaesthesia, Critical Care and Peri-operative Medicine, School of Medicine, Dentistry and Nursing, University of Glasgow, Glasgow, UK
2 Specialist Registrar, Department of Anaesthesia, Queen Elizabeth University Hospital, Glasgow, UK
3 Specialist Registrar, Departments of Emergency Medicine and Intensive Care Medicine, Queen Elizabeth University Hospital, Glasgow, UK
4 Foundation Doctor, 6 Professor, Department of Intensive Care Medicine, Glasgow Royal Infirmary, Glasgow, UK
8 Principal Clinical Physicist, NHS Greater Glasgow and Clyde, Glasgow, UK
9 Professor, The Healthcare Improvement Studies Institute, University of Cambridge, Cambridge, UK

Summary

Post-intensive care syndrome describes the physical, cognitive and emotional symptoms which persist following critical illness. At present there is limited understanding of the pathological mechanisms contributing to the development of post-intensive care syndrome. The aim of this systematic review was to synthesise current evidence exploring the association between inflammation and features of post-intensive care syndrome in survivors of critical illness. Relevant databases were systematically searched for studies of human participants exposed to critical illness. We sought studies that reported results for biomarkers with an identified role in the pathophysiology of inflammation obtained at any time-point in the patient journey and an outcome measure of any feature of post-intensive care syndrome at any point following hospital discharge. We included 32 studies, with 23 in the primary analysis and nine in a brain injury subgroup analysis. In the primary analysis, 47 different biomarkers were sampled and 44 different outcome measures were employed. Of the biomarkers which were sampled in five or more studies, interleukin-8, C-reactive protein and interleukin-10 most frequently showed associations with post-intensive care syndrome outcomes in 71%, 62% and 60% of studies, respectively. There was variability in terms of which biomarkers were sampled, time-points of sampling and outcome measures reported. Overall, there was mixed evidence of a potential association between an inflammatory process and long-term patient outcomes following critical illness. Further high-quality research is required to develop a longitudinal inflammatory profile of survivors of critical illness over the recovery period and evaluate the association with outcomes.

....

Introduction

Survival following critical illness is associated with a significant burden of morbidity and functional disability, which persists after patients have been discharged from the acute care setting [1]. Post-intensive care syndrome (PICS) describes the long-term consequences of critical illness [2].

Its symptoms are described in three domains: physical symptoms, such as fatigue, pain and weakness; cognitive symptoms, such as difficulty concentrating and memory impairment; and psychological symptoms, such as anxiety, depression and post-traumatic stress disorder. Over 60% of survivors report symptoms in one or more domain three months following discharge [3].

Post-intensive care syndrome has significant consequences for families, healthcare systems and society, in addition to those for the individual. For example, the reported prevalence of anxiety in family members of patients with critical illness is up to 80% [4]. In addition, over 50% of survivors are unable to return to employment in the year following hospital discharge [5], and up to 30% of survivors will require emergency readmission to hospital within 90 days of discharge [6]. However, despite the developing recognition of PICS, an understanding of the underlying mechanisms and pathophysiology is limited.

Systemic inflammation is a common feature of critical illness of various aetiologies and there is evidence to suggest that survivors continue to exhibit persistent low-grade inflammation following the resolution of acute illness [7, 8]. Additionally, inflammation has a well-described role in the pathophysiology of many other disease processes with symptoms common to PICS such as fatigue, pain, depression and cognitive impairment [9–11].

We hypothesised that inflammation may be what unites this diverse group of patients, pathologies and symptoms and may be associated with PICS. The aim of this systematic review was to synthesise current evidence evaluating the relationship between inflammation and the features of PICS in survivors of critical illness.

Methods

A systematic search was undertaken on Embase; Medline; Web of Science: Core Collection; CENTRAL; and PsychInfo (online Supporting Information Appendix S1). The original searches were performed on 26 October 2021 and updated on 22 January 2023. Results were not limited by date, but only English language results were included.

Inclusion criteria were all studies in human patients with critical illness. Studies were included if a biomarker which has an identified role in the pathophysiology of inflammation was obtained at any time-point in the patient journey, along with an outcome measure of any feature of PICS at any point following hospital discharge. Biomarkers could be sampled from any bodily fluid such as blood, sputum or cerebrospinal fluid (CSF). Studies were included if there was analysis exploring the association or relationship between the biomarker and outcome measure. Studies examining

patients with COVID-19 infection patients were also eligible for inclusion. Exclusion criteria were studies with neonatal or paediatric populations (age < 16 y), and studies with non-critical care populations. If articles had mixed adult and paediatric, or mixed critical care and non-critical care populations, they were eligible for inclusion if > 50% of patients were adults admitted to critical care. We excluded reviews; meta-analyses; case reports; case series; study protocols; conference abstracts; posters; and supplements.

Title and abstract screening were performed for all articles by two independent authors through Covidence (Melbourne, VIC, Australia) data management software. Any conflicts were resolved by consensus. Full-text review was performed for each article by two independent authors. If there was uncertainty regarding inclusion, attempts were made to contact the corresponding author for clarification. An independent reviewer resolved remaining conflicts.

Data extraction were carried out by one author and independently checked by a second. A data extraction template was created, collecting study design and demographics; participant characteristics; biomarker information; outcome measures; and association between biomarker and outcomes. If the relationship between the biomarker and outcome measure was unclear, then a single attempt was made to contact the corresponding author by email for clarification.

After discussion within the research team, meta-analysis was not deemed to be possible due to the heterogeneous nature of the inflammatory biomarkers sampled, study populations and outcome measures. At this stage, it also became clear that several studies focused on a sub-population of ICU patients with brain injuries (traumatic and atraumatic). As such it was deemed, from a clinical perspective, that the functional outcomes of this group of patients following hospital discharge were likely a reflection of the initial brain injury. As such, this cohort of patients formed a sub-group analysis.

Risk of bias assessment was performed by one author and independently checked by a second author. The Newcastle-Ottawa Scale for cohort studies was used for risk of bias assessment, which assesses studies in three domains: selection; comparability; and outcome [12]. The maximum possible score is nine, indicating a high-quality study. This was then converted to Agency for Healthcare Research and Quality (AHRQ) standards according to accepted thresholds [13].

Results

The initial database search retrieved 13,097 studies, of which 88 underwent full-text review. The updated search

retrieved 1833 additional studies, of which 14 underwent full-text review. In total, 32 studies were included: 23 of these were included in the primary analysis and the remaining nine in a subgroup analysis of the population of patients with a brain injury (Fig. 1). Details of study design for included studies are in Table 1 and online Supporting Information Table S1 and a summary of the included studies can be found in Table 2. Median (IQR [range]) Newcastle-Ottawa Scale score was 6.5 (5–7 [2–8]). Fifteen (47%) studies were rated as good, six (19%) were rated as fair and 11 (34%) studies were classified as poor according to AHRQ standards (online Supporting Information Table S2).

Two hundred different biomarkers of inflammation (or proteins associated with inflammatory pathways) were sampled across the 32 studies. Thirty-one studies evaluated biomarkers in blood or serum [14–44]; one study evaluated biomarkers in broncho-alveolar lavage samples [31]; and two studies evaluated biomarkers in CSF [25, 45].

In the primary analysis, 47 biomarkers were sampled in the 23 included studies. The most commonly sampled biomarkers were interleukin (IL)-6 (13 studies) [16, 19, 21, 25, 27, 28, 31, 32, 34, 35, 37, 38, 41]; C-reactive protein (CRP; 13 studies) [14, 15, 19–21, 25, 27, 30, 34, 40, 41, 43, 44]; IL-8 (seven studies) [19, 21, 27, 28, 31, 35, 41]; IL-1β (five studies) [19, 27, 34, 35, 41]; IL-10 (five studies) [19, 21, 32, 35, 41]; and procalcitonin (six studies) [23, 25, 30, 31, 38, 41]. A complete list of the biomarkers sampled is available in online Supporting Information Appendix S2. Of the 23 studies included in the primary analysis, 16 sampled biomarkers during hospital admission only (i.e. before outcomes of interest were measured) [14–16, 19–21, 23, 25, 28, 30, 31, 37, 38, 40, 41, 43]; two sampled biomarkers at post-discharge follow-up only (i.e. at the same time as outcomes of interest were measured) [17, 18]; and five sampled biomarkers both during hospital admission and at follow-up [27, 32, 34, 35, 44].

Of the biomarkers which were sampled in five or more studies, IL-8, CRP and IL-10 most frequently showed significant associations with PICS outcomes. Significant associations were seen in 5/7 [19, 21, 27, 28, 31], 8/13 [14, 15, 19, 20, 25, 27, 40, 44] and 3/5 [19, 21, 32] studies, respectively. Interleukin-6, procalcitonin and IL-1β each
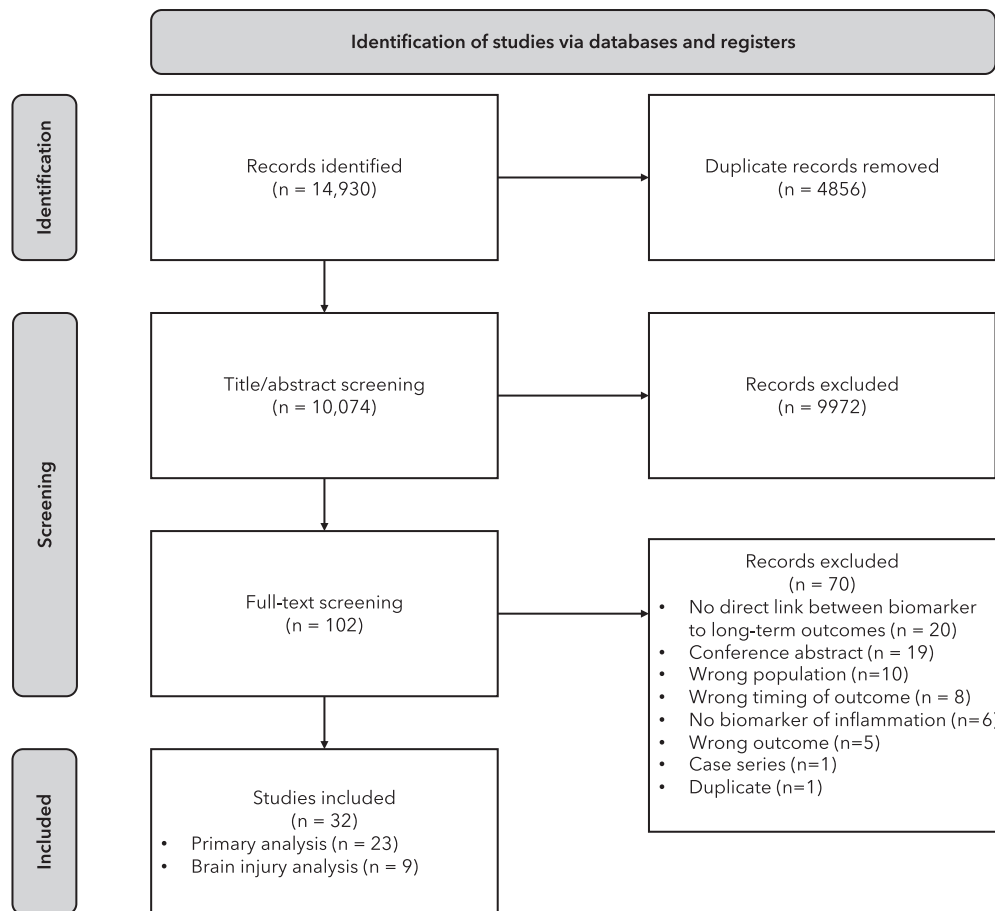

Figure 1 Study flow diagram.

Table 1 Characteristics of included studies.

	Studies n = 32
Geographical region	
USA	5
Germany	5
Sweden	3
Austria	2
Italy	2
Netherlands	2
UK	2
Turkey	2
India	1
Finland	1
Brazil	1
Switzerland	1
France	1
Belgium	1
China	1
Spain	1
Multiple	1
Prospective or retrospective	
Prospective	29
Retrospective	3
Study design	
Cohort study	28
Secondary analysis of a randomised controlled trial	4
Study scope	
Single-centre	23
Multicentre	9
Study population	
Mixed ICU	10
Brain injury	9
Sepsis	6
SARS-CoV-2	4
Trauma	1
Post-cardiac arrest	1
Peri-operative	1
Timing of outcome assessment	
1 month	1
3 months	8
6 months	12
12 months	9
> 12 months	2

showed significant associations in less than half of the studies in which they were sampled: 5/13 [19, 21, 25, 28, 32]; 2/6 [31, 38]; and 1/5 [19], respectively. Results for the most commonly sampled biomarkers in the primary analysis, stratified by subdomain are shown in Fig. 2 and online Supporting Information Table S3.

Eight studies in the primary analysis evaluated physical outcomes in survivors using 14 different outcome measures of physical health [14, 15, 18, 27, 28, 34, 40, 44]. Hand-grip strength and the 6-min walk test were the most commonly used outcome measures for this domain (each evaluated in three studies). A complete list of the outcome measures used for each domain is available in online Supporting Information Appendix S3.

Eight studies in the primary analysis evaluated cognitive symptoms in survivors of critical illness using 15 different cognitive outcome measures [17, 19, 20, 28, 32, 35, 41, 43]. The mini-mental state exam, cognitive failure questionnaire and trail-making test were the most commonly used outcome measures for this domain (each evaluated in two studies).

Three studies in the primary analysis evaluated emotional outcomes in survivors of critical illness using four different emotional outcome measures [28, 35, 37]. The impact of events scale-revised was the most commonly used outcome measure for this domain (evaluated in two studies).

Finally, 13 studies in the primary analysis evaluated global outcomes in survivors of critical illness with 11 different measures [16, 19, 21, 23, 25, 28, 30–32, 35, 37, 38, 40]. Global outcomes included quality of life and functional outcomes. The Barthel index was the most commonly used outcome measure for this domain (evaluated in three studies).

Relationship between inflammation and PICS

Of the eight studies which evaluated physical outcomes in the primary analysis, four measured inflammatory biomarkers during inpatient stay only [14, 15, 28, 40]; one at follow-up only [18]; and three both during inpatient stay and at follow-up [27, 34, 44]. Three studies did not find any association between the sampled biomarkers and outcomes [18, 28, 34], while five did [14, 15, 27, 40, 44]. Higher levels of the following were found to be associated with poorer physical health outcomes: CRP [14, 15, 27, 40, 44]; human neutrophil elastase [27]; IL-8 [27]; synaptotagmin-like protein-1 [27]; and soluble programmed death ligand-1 [44].

Of the eight studies that evaluated cognitive outcomes, five measured inflammatory biomarkers during inpatient stay only [19, 20, 28, 41, 43]; one at follow-up only [17]; and both during inpatient stay and at follow-up [32, 35]. Five studies did not find associations between the biomarkers sampled and cognitive outcomes [19, 28, 35, 41, 43]. The remaining three studies did, however, show significant associations between markers of inflammation and

Table 2 Summary of included studies.

Study	Population	No. of patients	PICS domain	Summary of results	Study quality[‡]
Baumbach et al. [14]	Mixed ICU	257	Physical	Association between CRP and pain severity and interference	Good
Baumbach et al. [15]	Mixed ICU	204	Physical	Association between CRP and incidence of chronic pain	Good
Brakenridge et al. [16]	Surgical sepsis	157	Global	Association between GLP-1 and functional outcomes	Good
Brück et al. [17]	Mixed ICU	100	Cognitive	Association between HMGB-1 levels and rapid visual information processing scores	Good
Brück et al. [18]	Mixed ICU	100	Physical	No significant associations	Good
Brummel et al. [19]	Mixed ICU	548	Cognitive and global	No association with long-term cognitive function. Consistent associations between CRP and MMP-9 and functional outcomes. Inconsistent associations between IL-1β; IL-6 IL-8; IL-10; TNF-α; and interferon-γ and functional outcomes	Good
Costas-Carrera et al. [20]	SARS-CoV-2	58	Cognitive	Association between high CRP days and Stroop interference score	Good
Darden et al. [21]	Surgical sepsis	349	Global	Consistent association between MCP-1; GLP-1; IL-8; IP-10 and sPDL-1 and functional outcomes. Inconsistent associations with IL-6; IL-10; GM-CSF; IGFBP3; angiopoeitin-2; SDF-1; sFLT-1 and VEGF	Fair
Deepika et al. [22]	Severe traumatic brain injury	89	Global	Association between IL-1β and IL-10 and functional outcomes	Good
Didriksson et al. [23]	SARS-CoV-2	498	Global	Association between lymphocytes and Glasgow outcome scale extended	Fair
Di Napoli et al. [24]	Spontaneous intracranial haemorrhage	210	Global	No significant associations	Fair
Ehler et al. [25]	Sepsis	21 (12 sepsis and 9 neurologic controls)	Global	Consistent association between serum IL-6 and functional outcomes. Inconsistent association between serum CRP and functional outcomes*	Poor
Gradisek et al. [26]	Traumatic brain injury	80	Global	Association between a cluster defined by elevated levels of these biomarkers and functional outcomes	Poor
Griffith et al. [27]	Mixed ICU	193	Physical	Human neutrophil elastase and CRP associated with mobility CRP, IL-8 and SLP-1 associated with lower hand-grip strength	Good
Hashem et al. [28]	Sepsis-associated ARDS	568	Physical; cognitive; emotional; and global	Association between the hyperinflammatory phenotype and mental health component summary of SF-36 and depression	Poor
Kiiski et al. [29]	Aneurysmal subarachnoid haemorrhage	47	Global	No significant associations	Poor
Krychtiuk et al. [30]	Cardiac arrest	53	Global	Association between the percentage of monocyte subsets and cerebral performance category outcomes	Fair

(continued)

Table 2 (continued)

Study	Population	No. of patients	PICS domain	Summary of results	Study quality[‡]
Lieberum et al. [31]	COVID-19	47	Global	Association between blood procalcitonin, TLR-3 and IL-8 and quality-of-life. Association between blood TLR-3 and functional outcomes	Good
Maciel et al. [32]	ICU	60	Cognitive and global	Association between IL-6 and IL-10 and long-term cognitive dysfunction	Good
Mazzeo et al. [33]	Traumatic brain injury	29	Global	Association between IL-2; IL-6; IL-8; IL-9; IL-10; IL-12; IL-13; IL-15; G-CSF; IP-10; MCP-1; MIP-1β; TNF-R2; VEGF and functional outcomes	Fair
Merriweather et al. [34]	ICU	193	Physical	No significant associations	Poor
Orhun et al. [35]	Sepsis	86	Cognitive; emotional; and global	No significant associations	Poor
Osthoff et al. [36]	Traumatic brain injury	44	Global	Association between ficolin-2, ficolin-3 and MASP-2 and functional outcomes	Good
Pastene et al. [37]	Trauma	157	Emotional and global	Association between sST-2 and health-related quality-of-life	Poor
Patejdl et al. [38]	Surgical ICU	15	Global	Association between procalcitonin and functional outcomes	Poor
Rass et al. [39]	Non-traumatic subarachnoid haemorrhage	297	Global	Association between SIRS[†] and functional outcomes	Fair
Santacruz et al. [45]	Brain injury	62 (acute brain injury n = 50; control n = 12)	Global	No significant associations	Poor
Sirayder et al. [40]	SARS-CoV-2	52 (26 SARS-CoV-2 patients and 26 healthy controls)	Physical and global	Association between CRP and forced vital capacity, dyspnoea, 6-min walk test and St George respiratory questionnaire	Poor
van den Boogaard et al. [41]	Mixed ICU	100	Cognition	No significant associations	Poor
Wang et al. [42]	Traumatic brain injury	106	Global	Association between HMGB-1, fibrinogen and CRP and functional outcomes	Good
Wolters et al. [43]	Mixed ICU	363	Cognitive	No significant associations	Good
Yende et al. [44]	Sepsis	483	Physical	Association between CRP and sPDL-1 and risk of mortality or readmission	Good

PICS, post-intensive care syndrome; CRP, C-reactive protein; GLP, glucagon-like peptide; HMGB, high mobility group box protein; MMP, matrix metallopeptidase; IL, interleukin; TNF, tumour necrosis factor; INF, interferon; MCP, monocyte chemoattractant protein; IP, interferon-γ-induced protein; sPDL, soluble programmed death ligand; GM-CSF, granulocyte-macrophage colony-stimulating factor; IGFBP, insulin-like growth factor binding protein; SDF, stromal cell-derived factor; sFLT, soluble vascular endothelial growth factor receptor; VEGF, vascular endothelial growth factor; SLP, synaptotagmin-like protein; SF, short form; TLR, toll-like receptor; MIP, macrophage inflammatory protein; MASP, mannan-binding lectin serine protease; sST, soluble suppression of tumorigenicity; SIRS, systemic inflammatory response syndrome.
*Data from additional analysis supplied by the authors on request. The authors note that this is underpowered.
[†]SIRS diagnosis based on white cell count.
[‡]Study quality determined by Agency for Healthcare Research and Quality standards.

cognitive outcomes [17, 20, 32]. Higher levels of IL-6 [32], IL-10 [32] and high mobility group box protein 1 [17] were found to be associated with poorer scores in certain cognitive health outcomes. Moreover, increased number of days with high CRP was associated with worse scores in certain cognitive outcomes [20].

Figure 2 Summary of associations found between the top six biomarkers and outcomes in each domain. Numbers in circles are references to studies, and the colours of the circles indicate whether an association was reported. Green circles, association reported; green and amber circles, inconsistent association reported; red circles, no association reported.

Of the three studies which evaluated emotional outcomes, all measured inflammatory biomarkers during hospital stay [28, 35, 37], and one study additionally measured biomarkers at follow-up [35]. Two studies did not find an association between inflammatory markers and outcomes [35, 37], but one showed an association between better emotional outcome scores and the hyperinflammatory phenotype at 12 months [28]. The defining characteristics of the hyperinflammatory phenotype include higher levels of IL-6; IL-8; soluble tumour necrosis factor receptor-1; and intercellular adhesion molecule-1; as well as lower levels of protein C [28, 46].

Thirteen studies evaluated the association between inflammation and global outcome measures. All measured inflammatory biomarkers during inpatient stay [16, 19, 21, 23, 25, 28, 30–32, 35, 37, 38, 40], and two studies additionally measured inflammatory biomarkers at follow-up [32, 35]. Three studies did not find any association [28, 32, 35] and the remaining 10 studies did. The global

outcome measures used in these studies could be generally subdivided into measures of disability or function, and measures of quality of life. Eight studies showed association between inflammation and measures of disability or function [16, 19, 21, 23, 25, 30, 31, 38]. Three studies found associations between inflammation and quality of life outcomes [31, 37, 40].

Higher levels of the following were associated with worse scores in certain global outcome measures: matrix metallopeptidase-9 [19]; IL-1β [19]; procalcitonin [31, 38]; glucagon-like peptide-1 [16, 21]; interferon-γ-induced protein-10 (IP-10) [21]; soluble programmed death ligand-1 [21]; soluble suppression of tumorigenicity-2 [37]; monocyte chemoattractant protein-1 [21]; angiopoietin-2 [21]; stromal-cell derived factor-1 [21]; and soluble vascular endothelial growth factor receptor-1 [21]. Moreover, one study showed worse outcomes in patients with higher levels of intermediate monocytes, which are defined as being positive for cluster of differentiation (CD)-14+; CD-16+; and C-chemokine receptor type 2 markers [30].

7

Higher levels of the following were associated with better scores in certain global outcome measures: lymphocyte count [23]; tumour necrosis factor-α [19]; interferon-γ [19]; granulocyte-macrophage colony-stimulating factor [21]; vascular endothelial growth factor [21]; toll-like receptor-3 [31]; and insulin-like growth factor binding protein-3 [21].

Additionally, four biomarkers showed positive associations with global outcomes in certain studies but negative associations in others. In two studies higher levels of CRP were associated with poorer outcomes [19, 40]; however, higher CRP levels were associated with better outcomes in a third study [25]. Higher levels of IL-6 were also associated with worse outcomes in two studies [19, 21] and better outcomes in another study [25]. Likewise, higher levels of IL-8 were associated with poorer outcomes in two studies [21, 31] and better outcomes in one study [19]. Finally, one study reported an association between IL-10 and worse outcomes [21], but a further study reported an association between IL-10 and better outcomes [19].

Patients with brain injury

Nine prospective cohort studies were included in the brain injury subgroup, all reporting global outcome measures [22, 24, 26, 29, 33, 36, 39, 42, 45]. A total of 172 biochemical markers of inflammation were sampled. The most commonly cited biomarkers were C-reactive protein and IL-6, each sampled in three studies. All studies sampled biomarkers during inpatient stay only.

All studies evaluated functional outcomes in the global domain. Three different outcome measures were used: modified Rankin Scale; Glasgow Outcome Scale; and the Extended Glasgow Outcome Scale. The latter was the most frequently used outcome measure (four studies).

Three studies did not find any association between biomarkers sampled and symptoms of PICS [24, 29, 45] but the remaining six did [22, 26, 33, 36, 39, 42]. Higher levels of the following were found to be associated with poorer scores in certain global outcome measures: IL-1β [22]; IL-10 [22, 33]; CRP [42]; high mobility group box protein-1 [42]; fibrinogen [42]; mannan-binding lectin serine protease-2 [36]; ficolin-2 [36]; ficolin-3 [36]; IL-2 [33]; IL-6 [33]; IL-8 [33]; IL-9 [33]; IL-12 [33]; IL-13 [33]; IL-15 [33]; granulocyte colony-stimulating factors [33]; interferon-γ-induced protein-10 [33]; monocyte chemoattractant protein-1 [33]; macrophage inflammatory protein-1β [33]; tumour necrosis factor-receptor-2 [33]; and vascular endothelial growth factor [33]. One study identified worse global outcomes in a cluster of patients defined by elevated levels of the following biomarkers: stem cell factor; fibroblast growth factor-19; fibroblast growth factor-23; glial cell line-derived neurotrophic factor; glial fibrillary acidic protein; and S100 calcium-binding protein B [26]. Moreover, another study found that global outcomes were poorer in the cohort of patients who exhibited systemic inflammatory response syndrome [39].

Discussion

This review highlights that there is mixed evidence of a potential association between an inflammatory process and long-term patient outcomes following critical illness. As a result, no definitive conclusions can be drawn. While various studies have shown a link between certain biomarkers of inflammation and outcomes in all domains of PICS, these results are generally inconsistent and several other studies reported that no association was seen. Of note, no single biomarker was able to be consistently and reproducibly shown to be associated with outcomes. In general, the literature was heterogeneous in terms of which biomarkers were sampled, time-points of sampling and outcome measures reported, impacting our ability to draw definitive conclusions. This suggests that further research is required to clarify the pathophysiological mechanisms underlying the development of PICS in order to establish potential therapeutic targets.

While many of the studies included in this review showed associations between certain biomarkers and outcome measures, these relationships were often inconsistent, both between and within studies. In certain studies, biomarkers were sampled at multiple time-points and showed associations with outcomes at one but not all points sampled. Moreover, there was a lack of consistency in associations shown when studies used multiple tests in the same domain. Several studies sampled the same biomarkers, and while some studies showed associations, others did not. For example, of the eight studies that evaluated the association between IL-6 and functional outcomes, only three found one [19, 21, 25]. Finally, inconsistencies were also seen in the directionality of the relationships, with certain studies reporting poorer outcomes associated with higher levels of certain biomarkers and other studies reporting improved outcomes associated with higher levels of the same biomarker. These inconsistencies could partly be explained by the heterogeneity seen in the populations studied and timings of biomarker sampling and outcome measurement. Of note, several of the cytokines evaluated in these studies, such as IL-1β, tumour necrosis factor-α and IL-6, are known to peak and decline within hours of the inflammatory

stimulus [47]. Timing of biomarker sampling therefore has significant potential to impact results.

While many studies in the primary analysis and the brain injury subgroup appeared to show an association between certain markers of inflammation and functional outcomes, the evaluation of this association is complex as many of the studies dichotomised their analysis of functional outcomes into `good´ or `poor´, where a poor outcome was considered as a hybrid outcome of death and severe disability. The scope of our review did not include mortality in the outcomes. It is, therefore, more complicated to establish whether inflammation is truly associated with PICS outcomes or whether this positive signal was attributable to excess mortality.

The studies included were of variable quality when assessed using the Newcastle-Ottawa Scale. However, several studies have additional limitations which are not accounted for in this assessment tool. The Newcastle-Ottawa Scale does not consider whether studies are prospective or retrospective or whether they are single-or multicentre studies. In addition, several of the studies included had a very small sample size and often the studies did not perform a power calculation. Moreover, many performed multiple tests without any statistical correction for this, leading to an increased risk of spurious results. This has the potential to contribute to difficulties interpreting results.

While the concept of inflammation being implicated in the development of PICS appears to be biologically plausible, the pathophysiology is likely complex. The aetiology of PICS is likely multifactorial, involving a complex interaction of disease, patient and environmental factors. The spectrum of PICS is vast and the specific symptoms reported by each patient are highly variable [3]. As such, there are likely multiple biochemical processes implicated, and the activation of certain pathways may be specific to certain populations of patients. Furthermore, while there has been extensive study of the inflammatory pathways implicated in the acute phase of critical illness, less is understood about pathways implicated in the longer-term recovery phase [7, 48]. Indeed, most of the studies included in this review explored the relationship between biomarkers of inflammation during the acute illness and long-term outcomes, with only a few studies sampling during the recovery phase. Further research should establish a detailed longitudinal inflammatory profile over the recovery trajectory in patients who have survived critical illness.

The societal burden of PICS is growing, given improved ICU survivorship rates and patients who are older and comorbid receiving critical care treatment, accelerating the development of frailty in these patients. Ultimately, it is hoped that by developing a greater understanding of the pathophysiological mechanisms contributing to the development of PICS, we can identify and develop therapies to help prevent this long-term morbidity. This review establishes a foundation on which this field can develop. The current position of this research has been clarified in this review as we have established which biomarkers and outcomes are being studied at what time-points, as well as the results. Future research should develop a detailed understanding of the longitudinal course of inflammation following recovery from critical illness and the pathways involved. High-quality prospective research can then target specific biomarkers to evaluate associations with PICS outcomes. However, hopes of identifying therapeutic targets need to be considered with caution given that the pathways involved are likely complex. Previously, several biological response modifiers have been trialled in acute critical illness due to sepsis, and none have yielded any proven benefit, likely due to failures in modelling the complexities of the underlying biochemical response to infection [49].

The limitations of this review are notable. Due to the inherent heterogeneity of the studies included and the scope and range of the biomarkers which were obtained, a meta-analysis was not possible. In addition, it was often impossible to determine whether the associations reflected a relationship between inflammation and functional outcomes in survivors when severe disability was grouped with mortality. Finally, there were three pairs of studies in this review which assessed the same population of patients ([14, 15], [17, 18] and [27, 34]), but as meta-analysis was not performed it was felt the impact of this was limited.

The aetiology of PICS is likely multifactorial and complex. There is mixed evidence to support the possible role of inflammation in the complex problems seen in survivors of critical illness. Further high-quality prospective research is required to develop a longitudinal inflammatory profile of survivors over the recovery period and evaluate the association with outcomes. A detailed understanding of the pathways involved is necessary to establish potential therapeutic targets.

Acknowledgements

References

1. Colbenson GA, Johnson A, Wilson ME. Post-intensive care syndrome: impact, prevention, and management. *Breathe* 2019; **15**: 98–101.

2. Needham DM, Davidson J, Cohen H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Critical Care Medicine* 2012; **40**: 502–9.

3. Marra A, Pandharipande P, Girard T, et al. Co-occurrence of post-intensive care syndrome problems among 406 survivors of critical illness. *Critical Care Medicine* 2018; **46**: 1393–401.

4. Johnson CC, Suchyta MR, Darowski ES, et al. Psychological sequelae in family caregivers of critically ill intensive care unit patients. A systematic review. *Annals of the American Thoracic Society* 2019; **16**: 894–909.

5. McPeake J, Mikkelsen ME, Quasim T, et al. Return to employment after critical illness and its association with psychosocial outcomes. A systematic review and meta-analysis. *Annals of the American Thoracic Society* 2019; **16**: 1304–11.

6. McPeake J, Bateson M, Christie F, et al. Hospital re-admission after critical care survival: a systematic review and meta-analysis. *Anaesthesia* 2022; **77**: 475–85.

7. Griffith DM, Vale ME, Campbell C, Lewis S, Walsh TS. Persistent inflammation and recovery after intensive care: a systematic review. *Journal of Critical Care* 2016; **33**: 192–9.

8. Bateman AP, McArdle F, Walsh TS. Time course of anemia during six months follow up following intensive care discharge and factors associated with impaired recovery of erythropoiesis. *Critical Care Medicine* 2009; **37**: 1906–12.

9. Kinney JW, Bemiller SM, Murtishaw AS, Leisgang AM, Salazar AM, Lamb BT. Inflammation as a central mechanism in Alzheimer's disease. *Alzheimer's and Dementia* 2018; **4**: 575–90.

10. Atzeni F, Nucera V, Masala IF, Sarzi-Puttini P, Bonitta G. Il-6 involvement in pain, fatigue and mood disorders in rheumatoid arthritis and the effects of il-6 inhibitor sarilumab. *Pharmacological Research* 2019; **149**: 104402.

11. Lee C-H, Giuliani F. The role of inflammation in depression and fatigue. *Frontiers in Immunology* 2019; **10**: 1696.

12. Wells G, Shea B, O'Connell D, et al. The Newcastle–Ottawa scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. 2021. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm (accessed 09/10/2023).

13. Parichehr S, Beryl Primrose G, Elena C, et al. Variation of effect estimates in the analysis of mortality and length of hospital stay in patients with infections caused by bacteria-producing extended-spectrum beta-lactamases: a systematic review and meta-analysis. *British Medical Journal Open* 2020; **10**: e030266.

14. Baumbach P, Götz T, Günther A, Weiss T, Meissner W. Prevalence and characteristics of chronic intensive care-related pain: the role of severe sepsis and septic shock. *Critical Care Medicine* 2016; **44**: 1129–37.

15. Baumbach P, Götz T, Günther A, Weiss T, Meissner W. Chronic intensive care-related pain: exploratory analysis on predictors and influence on health-related quality of life. *European Journal of Pain* 2018; **22**: 402–13.

16. Brakenridge SC, Moore FA, Mercier NR, et al. Persistently elevated glucagon-like peptide-1 levels among critically ill surgical patients after sepsis and development of chronic critical illness and dismal long-term outcomes. *Journal of the American College of Surgeons* 2019; **229**: 58–67.e1.

17. Brück E, Lasselin J, Caravaca AS, et al. Prolonged elevation of plasma HMGB1 is associated with cognitive impairment in intensive care unit survivors. *Intensive Care Medicine* 2020; **46**: 811–2.

18. Brück E, Svensson-Raskh A, Larsson JW, et al. Plasma HMGB1 levels and physical performance in ICU survivors. *Acta Anaesthesiologica Scandinavica* 2021; **65**: 921–7.

19. Brummel NE, Hughes CG, Thompson JL, et al. Inflammation and coagulation during critical illness and long-term cognitive impairment and disability. *American Journal of Respiratory and Critical Care Medicine* 2021; **203**: 699–706.

20. Costas-Carrera A, Sánchez-Rodríguez MM, Cañizares S, et al. Neuropsychological functioning in post-ICU patients after severe COVID-19 infection: the role of cognitive reserve. *Brain, Behaviour and Immunity - Health* 2022; **21**: 100425.

21. Darden DB, Brakenridge SC, Efron PA, et al. Biomarker evidence of the persistent inflammation, immunosuppression and catabolism syndrome (PICS) in chronic critical illness (CCI) after surgical sepsis. *Annals of Surgery* 2021; **274**: 664–73.

22. Deepika A, Devi BI, Shukla D, Sathyaprabha TN, Christopher R, Ramesh SS. Neuroimmunology of traumatic brain injury: a longitudinal study of interdependency of inflammatory markers and heart rate variability in severe traumatic brain injury. *Journal of Neurotrauma* 2018; **35**: 1124–31.

23. Didriksson I, Leffler M, Spångfors M, et al. Intensive care unit burden is associated with increased mortality in critically ill COVID-19 patients. *Acta Anaesthesiologica Scandinavica* 2023; **67**: 329–38.

24. Di Napoli M, Godoy DA, Campi V, et al. C-reactive protein level measurement improves mortality prediction when added to the spontaneous intracerebral hemorrhage score. *Stroke* 2011; **42**: 1230–6.

25. Ehler J, Saller T, Wittstock M, et al. Diagnostic value of NT-proCNP compared to NSE and S100B in cerebrospinal fluid and plasma of patients with sepsis-associated encephalopathy. *Neuroscience Letters* 2019; **692**: 167–73.

26. Gradisek P, Carrara G, Antiga L, et al. Prognostic value of a combination of circulating biomarkers in critically ill patients with traumatic brain injury: results from the European CREACTIVE Study. *Journal of Neurotrauma* 2021; **38**: 2667–76.

27. Griffith DM, Lewis S, Rossi AG, et al. Systemic inflammation after critical illness: relationship with physical recovery and exploration of potential mechanisms. *Thorax* 2016; **71**: 820–9.

28. Hashem MD, Hopkins RO, Colantuoni E, et al. Six-month and 12-month patient outcomes based on inflammatory subphenotypes in sepsis-associated ARDS: secondary analysis of SAILS-ALTOS trial. *Thorax* 2022; **77**: 22–30.

29. Kiiski H, Jalkanen V, Ala-Peijari M, Hämäläinen M, Moilanen E, Peltola J, Tenhunen J. Plasma soluble urokinase-type plasminogen activator receptor is not associated with neurological outcome in patients with aneurysmal subarachnoid hemorrhage. *Frontiers in Neurology* 2017; **8**: 144.

30. Krychtiuk KA, Lenz M, Richter B, et al. Monocyte subsets predict mortality after cardiac arrest. *Journal of Leukocyte Biology* 2021; **109**: 1139–46.

31. Lieberum JN, Kaiser S, Kalbhenn J, Bürkle H, Schallner N. Predictive markers related to local and systemic inflammation in severe COVID-19-associated ARDS: a prospective single-center analysis. *BMC Infectious Diseases* 2023; **23**: 19.

32. Maciel M, Benedet SR, Lunardelli EB, et al. Predicting long-term cognitive dysfunction in survivors of critical illness with plasma inflammatory markers: a retrospective cohort study. *Molecular Neurobiology* 2019; **56**: 763–7.

33. Mazzeo AT, Filippini C, Rosato R, et al. Multivariate projection method to investigate inflammation associated with secondary insults and outcome after human traumatic brain injury: a pilot study. *Journal of Neuroinflammation* 2016; **13**: 157.

34. Merriweather JL, Griffith DM, Walsh TS. Appetite during the recovery phase of critical illness: a cohort study. *European Journal of Clinical Nutrition* 2018; **72**: 986–92.

35. Orhun G, Tüzün E, Özcan PE, et al. Association between inflammatory markers and cognitive outcome in patients with acute brain dysfunction due to sepsis. *Nöro Psikiyatri Arşivi* 2019; **56**: 63–70.

36. Osthoff M, Walder B, Delhumeau C, Trendelenburg M, Turck N. Association of lectin pathway protein levels and genetic variants early after injury with outcomes after severe traumatic brain injury: a prospective cohort study. *Journal of Neurotrauma* 2017; **34**: 2560–6.

37. Pastene B, Cinotti R, Gayat E, et al. Long-term mortality and quality of life after trauma: an ancillary study from the prospective multicenter trial FROG-ICU. *European Journal of Trauma and Emergency Surgery* 2021; **47**: 461–6.

38. Patejdl R, Walter U, Rosener S, Sauer M, Reuter DA, Ehler J. Muscular ultrasound, syndecan-1 and procalcitonin serum levels to assess intensive care unit-acquired weakness. *Canadian Journal of Neurological Sciences* 2019; **46**: 234–42.

39. Rass V, Gaasch M, Kofler M, et al. Systemic inflammatory response syndrome as predictor of poor outcome in nontraumatic subarachnoid hemorrhage patients. *Critical Care Medicine* 2018; **46**: e1152–9.

40. Sirayder U, Inal-Ince D, Kepenek-Varol B, Acik C. Long-term characteristics of severe COVID-19: respiratory function, functional capacity, and quality of life. *International Journal of Environmental Research and Public Health* 2022; **19**: 6304.

41. van den Boogaard M, Kox M, Quinn KL, van Achterberg T, van der Hoeven JG, Schoonhoven L, Pickkers P. Biomarkers associated with delirium in critically ill patients and their relation with long-term subjective cognitive dysfunction; indications for different pathways governing delirium in inflamed and noninflamed patients. *Critical Care* 2011; **15**: R297.

42. Wang K-Y, Yu G-F, Zhang Z-Y, Huang Q, Dong X-Q. Plasma high-mobility group box 1 levels and prediction of outcome in patients with traumatic brain injury. *Clinica Chimica Acta* 2012; **413**: 1737–41.

43. Wolters AE, Peelen LM, Veldhuijzen DS, et al. Long-term self-reported cognitive problems after delirium in the intensive care unit and the effect of systemic inflammation. *Journal of the American Geriatrics Society* 2017; **65**: 786–91.

44. Yende S, Kellum JA, Talisa VB, et al. Long-term host immune response trajectories among hospitalized patients with sepsis. *Journal of the American Medical Association Network Open* 2019; **2**: e198686.

45. Santacruz CA, Vincent J-L, Duitama J, et al. The cerebrospinal fluid proteomic response to traumatic and nontraumatic acute brain injury: a prospective study. *Neurocritical Care* 2022; **37**: 463–70.

46. Sinha P, Delucchi KL, Thompson BT, McAuley DF, Matthay MA, Calfee CS. Latent class analysis of ARDS subphenotypes: a secondary analysis of the statins for acutely injured lungs from sepsis (SAILS) study. *Intensive Care Medicine* 2018; **44**: 1859–69.

47. Calder PC, Ahluwalia N, Albers R, et al. A consideration of biomarkers to be used for evaluation of inflammation in human nutritional studies. *British Journal of Nutrition* 2013; **109**: S1–S34.

48. Hawkins RB, Raymond SL, Stortz JA, et al. Chronic critical illness and the persistent inflammation, immunosuppression, and catabolism syndrome. *Frontiers in Immunology* 2018; **9**: 1511.

49. Angus DC, van der Poll T. Severe sepsis and septic shock. *New England Journal of Medicine* 2013; **369**: 840–51.

Supporting Information

Additional supporting information may be found online via the journal website.

Appendix S1. Example search strategy.

Appendix S2. Complete list of biomarkers sampled.

Appendix S3. Complete list of outcome measures stratified by domain.

Table S1. Risk of bias assessment.

Table S2. Full results.

Table S3. Summary associations for top six biomarkers.