Quantifying the burden of the post-ICU syndrome in South Africa: A scoping review of evidence from the public health sector

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Background. The post-ICU syndrome (PICS) comprises unexpected impairments in physical, cognitive, and mental health after intensive care unit (ICU) discharge, and is associated with a diminished health-related quality of life (HRQOL). A Cochrane review recommended more research in this field from low- and middle-income countries.
Objective. This review aims to examine the extent and nature of publications in the field of PICS in the South African (SA) public health sector. Findings of available local research are contextualised through comparison with international data.
Methods. A comprehensive literature search strategy was employed. Inclusion criteria comprised publications enrolling adult patients following admission to SA public hospital ICUs, with the aim to study the main elements of PICS (ICU-acquired neuromuscular weakness, neurocognitive impairment, psychopathology and HRQOL).
Results. Three studies investigated physical impairment, 1 study psychopathology, and 2 studies HRQOL. Recommended assessment tools were utilised. High rates of attrition were reported. Neuromuscular weakness in shorter-stay patients had recovered at 3 months. Patients who were ventilated for ≥5 days were more likely to be impaired at 6 months. The study on psychopathology reported high morbidity. The HRQOL of survivors was diminished, particularly in patients ventilated for ≥5 days.
Conclusion. This review found a paucity of literature evaluating PICS in the SA public health sector. The findings mirror those from international studies. Knowledge gaps pertaining to PICS in medical, surgical and HIV-positive patients in SA are evident. No publications on neurocognitive impairment or the co-occurrence of PICS elements were identified. There is considerable scope for further research in this field in SA.
Keywords: Post intensive care syndrome, critical care, South Africa, review, anxiety disorder, depressive mood disorder, post-traumatic stress disorder, health-related quality of life, physical impairment, neurocognitive impairment, ICU-acquired neuromuscular weakness.

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Contribution of the study
This review identified the available publications investigating the post ICU syndrome (PICS) in the South African public healthcare setting. A small number of ground-breaking studies were found. Knowledge gaps in this field were identified.

Improved life expectancy, together with advances in life support technologies, has resulted in intensive care unit (ICU) care being offered to increasingly more patients. However, the improved survival is often achieved at a high cost and prolonged ICU admission. Taking into account the presence of comorbidities and need for long ICU stays, coupled with the cost of care, the long-term quality of life post-ICU has come into question.

The post-ICU syndrome (PICS), a constellation of unexpected new or worsened impairments in physical, cognitive, and/or psychological health which persist after critical care discharge, has been well described in studies from high-income countries (HICs).[1] Among ICU survivors, health-related quality of life (HRQOL) is often diminished because of the presence of one or more aspects of PICS. There is paucity of such data from low- and middle-income countries (LMICs), prompting a recent Cochrane review to recommend additional research in a wider variety of resource settings.[2]

The call is justified since significant differences exist between ICU patient populations in HICs and LMICs, such as South Africa (SA). Firstly, the mean age of SA ICU populations is ~10 - 20 years younger than that reported in HICs.[3-12] A higher age is associated with more comorbidities and frailty, which may influence the incidence of PICS. Secondly, most ICU follow-up studies from HICs emanate from multidisciplinary ICUs, with the majority of cases comprising medical admissions and smaller subsets of emergency surgical and trauma patients.[5-7,9,11-13] In contrast, SA multidisciplinary ICUs in the public sector report a higher proportion of surgical emergency admissions with a preponderance of trauma-related admissions.[3,4,14] Another notable difference relates to the incidence of people living with HIV. In 2017, 56% of admissions to a tertiary Eastern Cape ICU were tested for HIV, of whom 33% were HIV-positive.[3] While the effect of HIV status on PICS is unknown, it is known that HIV-associated neurocognitive impairment typically causes impairments which are

similar to the cognitive impairment found in PICS.[15-17] Furthermore, a lower socioeconomic status is also associated with a lower self-reported HRQOL,[18] which can impact on PICS assessment in LMICs. Closely linked to socioeconomic factors is the level of education. A large cohort study identified a positive relationship between the level of education, socioeconomic status and the ability to remain PICS-free.[7] Finally, the trajectory of recovery after critical illness is enhanced by rehabilitation and appropriate psychological support. Such services remain inadequate in many regions of the SA public healthcare landscape and may preclude appropriate follow-up, diagnosis and treatment of patients with PICS.[19] There are no dedicated public sector rehabilitation facilities in certain provinces, so rehabilitation can only take place on an outpatient basis, or alternatively, within the existing acute-care setting where considerable bed pressure is evident. This poses a problem for disabled patients who may not have access to private or public transport. The resource challenges related to mental health services in SA have also been well documented.[20] Furthermore, there are vast resource differences between the public and private healthcare sectors in SA.[21,22] SA is unique among the LMICs, including other sub-Saharan African LMICs and BRICS countries (Brazil, Russia, India, China, and South Africa), with documented differences in genetic and disease profiles, health systems and economy.[23-28]

In light of these differences pertaining to patient characteristics, admission profile, socioeconomic status, educational level, comorbidities, access to healthcare and post-ICU support, the observations related to PICS from other countries clearly cannot necessarily be extrapolated to SA. The objective of this review is to examine the extent and nature of research conducted in the field of PICS in the SA public health sector with the aim of identifying knowledge gaps. Furthermore, the findings from available SA data are contextualised through comparison with international data in the discussion.

Methods

The stepwise process advocated by Arksey and O'Malley[29] and PRISMA Extension for Scoping Reviews[30] was followed: (*i*) identifying the research question; (*ii*) identifying relevant studies; (*iii*) study selection; (*iv*) charting the data; and (*v*) collating, summarising and reporting results. The research question is: what is the extent, nature and main findings of studies in the field of PICS emanating from the SA public health sector? Inclusion criteria comprised publications which enrolled adult patients who were followed up after admission to SA public hospital ICUs, with the aim to study any of the main elements of PICS. These elements include physical impairment (ICU-acquired neuromuscular weakness in particular), neurocognitive impairment, post-traumatic stress disorder (PTSD), anxiety, depressive mood disorder and HRQOL. Exclusion criteria comprised studies which enrolled cohorts of neurosurgical, spinal and stroke patients as well as personal narratives, commentaries and qualitative studies. The rationale for excluding the aforementioned diagnostic categories relates to there being existing rehabilitation pathways for patients with such conditions, and because their post-discharge disability may relate more to their primary diagnosis rather than to PICS. Studies from the private healthcare sector were excluded because of the differences in resources, including rehabilitation facilities.

A comprehensive literature search strategy was employed. The following search terms were used in combination: South Africa, intensive care unit, intensive care, critical care, survivor(s), follow up/follow-up clinic, post intensive care syndrome, anxiety disorder, depressive mood disorder, post-traumatic stress disorder, health-related quality of life, psychological impairment, physical impairment, neurocognitive impairment & sequelae, frailty, ICU-acquired neuromuscular weakness, and rehabilitation services. Search terminology included controlled vocabulary terms and keywords as necessary to achieve the best retrieval from each database. The above terms were combined with observational and randomised control trial study designs and limited to the English language.

Six computerised bibliographic databases were searched by the primary investigator, namely Medline PubMed, CINAHL, Science Direct, Ovid MEDLINE, Google Scholar and the University of Cape Town library (from inception until 1 December 2021). Bibliographies and references of relevant articles were further screened for other relevant studies. Titles and abstracts were screened for relevancy by EvdM. South African researchers known to have published research in the relevant field were contacted to ensure inclusion of their work. All available publications were screened by EvdM for inclusion.

The included publications were organised according to the main aspects of PICS, namely, physical impairment, psychopathology, neurocognitive impairment and HRQOL.

Results

Taking into account the different components of PICS, and the variety of terms used to describe these, a large number of records had to be screened for relevance (3 449). The titles, and where necessary the abstracts, were screened for eligibility. Sample heterogeneity was supported using a scoping review method. Fig. 1 depicts the process of screening and selection of included publications. Three publications were excluded, one for conduct in the private sector,[31] one for conduct in both the private and public sector without patient differentiation,[32] and a personal account.[33] Six SA publications conducted among five cohorts were eligible for inclusion. The publications included in this review are summarised in Table 1.

Physical impairment

As depicted in Table 1, three publications evaluating physical impairment were identified, including two pilot trials. In the first pilot trial, 12 patients, ventilated for a mean (standard deviation (SD)) duration of 14.5 (9.27) days following penetrating trunk injury, were evaluated for physical impairment on follow-up.[34] Dynamometry measurements for upper and lower limbs and the 6-minute-walk test (6MWT) distance were compared with those of 12 healthy, matched volunteers. Upper limb strength matched the controls' strength at 3 months, while lower limb strength only recovered by 6 months. Although the 6MWT distance increased by 10% for the study group over the 6-month period, it still remained significantly less than the distance walked by the control group. The pulmonary function tests (PFTs) were measured mostly within 80% of the predicted values. The criteria for $VO_{2maximum}$ were not met and the $VO_{2\ peak}$ improved only marginally (12%) over 6 months.

Van Aswegen *et al.*[35] subsequently followed the abovementioned pilot trial with a longitudinal case-control study in a similar patient population. The cohort was categorised as long ventilation (LV) and short ventilation (SV) groups (≥5 v. <5 days). The mean (SD) number of days of mechanical ventilation (MV) for the SV group was significantly shorter than the LV group (2.3 (1.1) v. 19.5 (13.4), $p< 0.00$). At 6-month follow-up, MV for ≥5 days and a higher severity of illness were found to be risk factors for physical impairment as witnessed by a lower 6MWT distance and a poor PCS (Physical Component Summary score of the Short Form-36 health-related quality of life questionnaire).[35] A notable finding of this study was that SV subjects had recovered

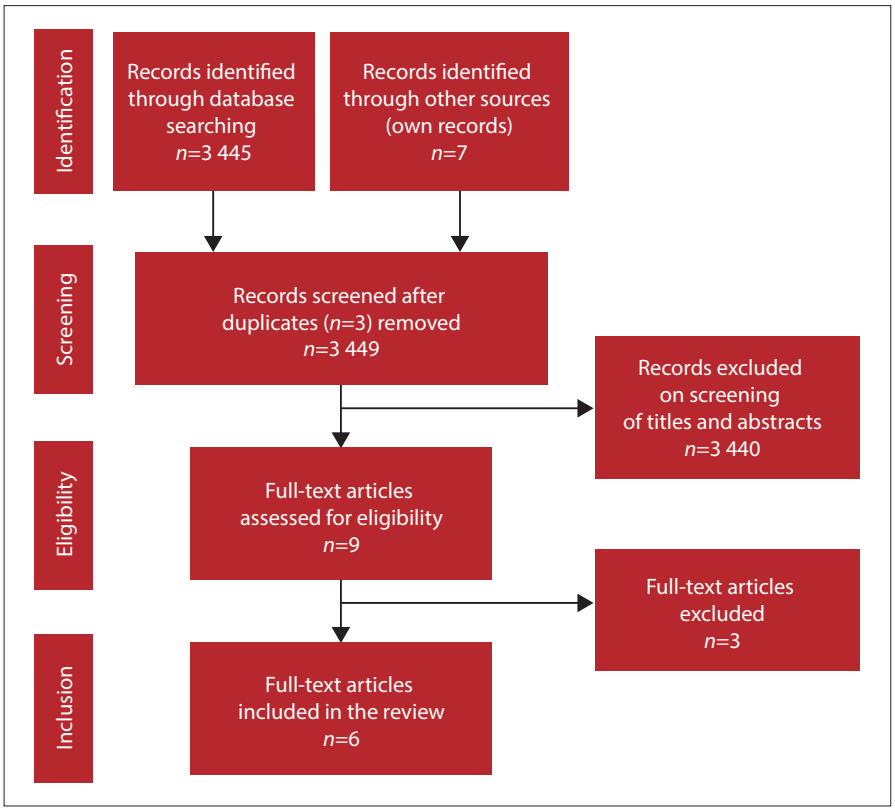

Fig. 1. Process of screening and selection of included publications.

within 3 months post discharge with regard to exercise capacity, muscle strength and HRQOL. This was in contrast to the LV group, who demonstrated significant limitations in exercise capacity, muscle strength and the PCS up to 6 months after discharge. PFTs were normal on follow-up and there was no change in oxygen uptake on follow-up; the authors concluded that this indicated that physical impairment was largely related to neuromuscular weakness. The authors noted a high rate of attrition among the cohort (45%) with an even higher attrition rate in the SV subgroup (54%).

The second pilot study enrolled 5 patients, all of whom were HIV-positive and ICU survivors, among whom only 2 completed 6-month follow-up.[36]

Psychopathology

A single study investigating the psychological sequelae in SA ICU survivors was identified. Hatchett *et al.*[37] recruited 98 patients on return to outpatient departments between 1 and 4 months after ICU discharge. In spite of the fact that only 34% had been mechanically ventilated, 28% demonstrated symptoms of depression, 48% presented with anxiety and 32% showed signs of PTSD. Patients who had memories of physical restraint were 6 times more likely to develop PTSD symptoms.

HRQOL

Two SA studies examining the HRQOL among public sector critical care survivors in SA were identified. Both were conducted among patients who were admitted to ICU following surgery and/or trauma and both utilised the Medical Outcomes Short Form 36 (SF-36) questionnaire as study tool.[38,39]

Van Aswegen *et al.*[35,38] investigated the HRQOL among the same cohort who were followed up for 6 months for physical impairment. Firstly, the SV group's HRQOL scores were compared with their own baseline scores, as well as with the scores from a healthy control group. Both the SV group's physical component summary (PCS) and mental component summary (MCS) scores were significantly lower at 1 and 3 months as compared with their baseline. In the SV group the PCS, but not the MCS, had returned to their baseline score by 6 months. When the SV group's MCS and PCS scores at 6 months were compared with those of a healthy control group, no significant differences were found. The authors state that these findings should be interpreted with caution in view of the high rate of attrition in the SV group (54%). The LV group's PCS and MCS scores were significantly lower at 1, 3 and 6 months when compared with the baseline scores. When compared with the healthy control group's scores, the 6-month PCS was reported to be lower, but not the MCS score. In summary, the SV group had largely recovered their PCS score by 6 months while the LV group still had low scores at the same point in time. The authors concluded that subjects who had greater morbidity and prolonged MV, suffered from reduced HRQOL for up to 6 months after discharge. In the comparison with the control group, it appears that the MCS may have returned to baseline more quickly. There was a discrepancy noted in that both groups' MCS scores were low when compared with their own retrospective baseline but not when compared with the control group's scores. The authors suggest that this may have been due to recall bias.

Karachi *et al.*[39] evaluated the 12-month post-discharge HRQOL of 46 patients admitted to a surgical ICU, with emergency surgery comprising more than half of the cohort, followed by elective surgery and trauma. The interviews were conducted telephonically. Of the cohort only 28.3% of patients were ventilated and the self-reported HIV status was documented in 45.7% of cases, all of whom were reported as negative. The 12-month mean (SD) PCS score was reported to be 45.8 (10) and the MCS 49.1 (10.4), with the authors concluding that the scores of this surgical ICU population were much lower than international populations studied. The comparator populations are not specified. A higher age and APACHE II score were significantly associated with lower physical and social functioning scores.

Discussion

This review found limited, albeit ground-breaking, publications examining the PICS in ICU survivors from SA public hospitals. These included a pilot study and a subsequent follow-up study comprising 42 patients, both of which explored the physical limitations in young, predominantly male patients with penetrating trunk trauma.[34,35] One study examined psychological sequelae[37] and two publications reported on the HRQOL of trauma and surgical patients who survived ICU.[38,39] No studies on neurocognitive impairment following ICU admission were identified.

All of the aforementioned studies, although numerically restricted, utilised internationally recommended measurement tools for the follow-up of ICU survivors.[40] A limitation, when studying certain aspects of PICS in SA, is the lack of population norms for muscle

Table 1. Publications included

First author and year published	Follow-up visits	Participant number & attrition *N/n* (%)	Study population	Study tools	Study design
Physical impairment					
Van Aswegen *et al.*, 2008[34]	1, 3 & 6 months	12/3 (25)	Penetrating trunk trauma; 95% male	6MWT, dynamometry, PFT, VO2	Pilot study. Prospective observational study combined with case-control study
Van Aswegen *et al.*, 2010[35]	1, 3 & 6 months	42/19 (45)	Penetrating trunk trauma; 92% male	6MWT, dynamometry, PFT, VO2, SF-36 PCS	Prospective observational study combined with case-control study
Roos *et al.*, 2021[36]	6 months	5/3 (60)	HIV-positive medical patients	6MWT, Karnofsky Performance Status Scale, EQ-5D-3 L, VAS	Pilot study. Prospective observational
Psychopathology					
Hatchett *et al.*, 2010[37]	Single interview ranging between 4 weeks to 4 months	98 (not applicable)	Mixed surgical – medical ICU patient population	HADS and ETIC-7	Observational study. Enrolled at outpatient follow-up
Health-related quality of life					
Van Aswegen *et al.*, 2011[38]	1, 3 & 6 months	42/19 (45%)	Penetrating trunk trauma; 92% male	SF-36	Prospective observational study combined with case-control study
Karachi *et al.*, 2011[39]	12 months	46 (not applicable)	Surgical and trauma cases	SF-36	Observational study, enrolled at 12-month telephonic interview

6MWT = 6-minute walk test; PFT = pulmonary function test; VO_2 = oxygen uptake; SF-36= Short Form-36 health-related quality of life questionnaire; PCS = the Physical Component Summary score of the Short Form-36 health-related quality of life questionnaire; EQ-5D-3 L= EuroQol-5 dimensions-3 levels; VAS = Visual Analogue Scale; HADS = Hospital Anxiety and Depression Scale; ETIC-7 = Experience after Treatment in ICU-7 scale.

strength as measured by dynamometry, the SF-36 questionnaire and the 6MWT. This limitation was overcome in some of the studies by employing a case-control study design and/or by comparing the changes in patients' measurements over time.[34,35,38]

Physical impairment

The work by Van Aswegen *et al.*[34,35] included a specific subset of ICU patients, i.e. largely young males with penetrating trunk trauma. They demonstrated that length of ventilation is a predictor for persisting neuromuscular weakness at 6 months. The severity of disease and incidence of sepsis and organ failure were reported to be significantly higher in the LV group and these factors have also all been found to be risk factors for ICU-acquired weakness in various other international reviews.[41-43] The high 6-month attrition rate of 45%, which was even higher in the SV subgroup, may reflect the fact that younger patients who had recovered did not see the need to return for follow-up. Future study design in SA should take this into consideration.

Psychopathology

The high reported incidence of symptoms of depression (28%), anxiety (48%) and PTSD (32%) in the SA publication[37] is in keeping with previous findings. Various systematic reviews and studies reported that the prevalence in ICU survivors ranged between 17% and 46% for symptoms of depression, 23% and 48% for symptoms of anxiety, and 8% and 35% for symptoms of PTSD symptoms.[12,13,44-50]

The cross-sectional study design, where patients were enrolled at follow-up visits, had the limitation that patients were screened at different periods post discharge and that not all eligible ICU patients were assessed. As acknowledged in the study, selection bias may have been introduced as a lack of drive and avoidance may have led to non-attendance at follow-up visits. Prospective enrolment of patients creates the opportunity to explain to patients the risk of PICS and to provide them with written information about PICS to take home. Furthermore, prospectively enrolled patients can be reminded of scheduled follow-up visits; this affords them the opportunity to reschedule if needed. The notable finding that physical restraints during the ICU stay may correlate with the development of PTSD symptoms has also been described previously.[51]

HRQOL

The limited SA public sector data from largely young, previously well males following physical trauma, points towards a prolonged poor physical HRQOL in those who have higher disease severity, are older and have longer ICU stays. These findings are aligned with the findings from an older systematic review of HRQOL in ICU survivors,[52] as well as a more recent systematic review which found that diagnostic categories, including the acute respiratory distress syndrome, prolonged ventilation, severe trauma and sepsis, were predictive of impairments in long-term HRQOL.[53] Young patients who were ventilated for <5 days recovered more quickly. These findings are also in keeping with those from international studies that younger critical care survivors with less comorbidity required shorter timeframes to return to independence.[52,54-56] Recovered patients may not be motivated to attend follow-up and this may explain the high rate of attrition. This should be factored in when planning follow-up studies in SA. The mental health components of HRQOL may be less affected than the physical aspects, or recovery may occur more quickly. This is similar to previous findings, with the authors speculating that the quicker recovery in the mental health domains may be attributed to a mental high in their subjects 'as they had cheated death'.[57]

Previous studies have demonstrated that the ICU survivor's premorbid HRQOL has a significant effect on the post-discharge HRQOL, and therefore, in order to minimise bias, it is recommended that the pre-ICU admission HRQOL should also be measured

for comparison.[58-60] As expected, a poor pre-ICU HRQOL also correlates with lower scores on follow-up after discharge.[57,60,61] A large systematic review of the long-term HRQOL of ICU survivors observed that <20% of studies reported the premorbid HRQOL and this was considered a limitation in terms of interpreting the outcomes.[53] Although recall bias may influence the results, this is not considered sufficient reason for not measuring the baseline HRQOL.[62] Van Aswegen *et al*.[38] speculated that recall bias (where survivors over-estimate their premorbid HRQOL) may have explained the discrepancy between when the comparator was a control group v. when the patient's own historical baselines were used. However, the high attrition rate may have also accounted for this finding, as this phenomenon was not observed in a larger international study.[63]

General comments

Quantifying the PICS burden is imperative, taking into account the costly resources invested in ICU therapy, as well as the potential to implement preventive strategies and improve patients' outcomes. There is a paucity of local literature on PICS in the SA public health sector setting, where the ICU population is characteristically unique in comparison with HICs. The available cohorts included in this review, although numerically restricted, highlight that PICS certainly exists in SA and that the reported findings appear to mirror observations from HICs. Further, we have identified specific data gaps in the context of PICS, which demarcates the way for further PICS-related research in the SA public sector ICUs. A limitation of this study is the varied terms and keywords used in studies of the various elements of PICS. The authors have included a large number of search terms and keywords but it is possible that eligible studies may have been missed. A further limitation is posed by the fact that only one author was involved with screening of articles for inclusion in the review without a validation by the other author.

SA data should ideally emanate from larger cohorts which are also inclusive of medical, general trauma and emergency surgical patients. The effect of HIV serostatus on PICS in particular warrants further exploration. Furthermore, there is no work in SA on the neurocognitive after-effects of critical illness and ICU admission. Lastly, there is also no published work from SA regarding the co-occurrence of the elements of PICS, and thus far, all the available data originate from Gauteng and the Western Cape provinces.

Determining the incidence of PICS symptoms has implications for the introduction or re-engineering of rehabilitation resources and ICU follow-up services. In the SA public health sector, ICU resources are limited.[64] We grapple daily with decision-making and prognosticating about which patients will benefit most from ICU treatment. Long-term outcomes such as HRQOL are therefore important in order to assess the effect and true value of this costly therapy in the SA population. Lastly, research in this field will assist in identifying and profiling PICS characteristics to non-intensivist clinicians, surviving patients, patient families, allied healthcare professionals and the public. This would be an important step towards developing support structures, addressing the psychological and mental health of, and improving the understanding of the condition for, the growing cohort of ICU survivors.

The COVID-19 pandemic has served to highlight and promote research and education on the long-term effects of critical illness and PICS.[65] Although there is no published information on the existence of dedicated ICU follow-up clinics in the SA public sector, certain tertiary centres are now following up COVID-19 patients with the aim of identifying PICS and long- COVID symptoms.

Conclusion

The limited available publications in the field of PICS in the SA public health sector point towards a high burden of mental health problems and physical impairment among long-stay patients, mirroring the findings from international studies. More data need to be collected regarding all the aspects of PICS (physical impairment, neurocognitive functioning, mental health and HRQOL) among general trauma patients, medical patients, HIV-positive patients, and surgical patients. There is a high attrition rate among young men, particularly in the subset who have short ICU stays. This should inform the design of future studies. Strategies to minimise attrition, such as prospective enrolment, the provision of PICS information and assistance with transport, should be considered. In view of the absence of SA population norms for certain measurements, determining the retrospective preadmission function and/or comparing patients with matched controls may be needed.

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