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Long-term outcomes and associated factors among intensive care unit survivors in a low-income country: a multicenter prospective cohort study

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Abstract

Objective Post-ICU survivors face higher mortality and often require costly rehabilitation or palliative care, such as occupational therapy, physiotherapy and hospice. However, there is a lack of data quantifying the demand for these services, particularly in developing countries like Uganda. Therefore, this prospective cohort study aimed to investigate the 90-day mortality rate, functional status, and mortality risk factors among 121 ICU patients discharged from three tertiary hospital ICUs in Uganda by tracking their vital and physical functional status for three months with follow-ups on days 30, 60, and 90, and identifying risk factors through Cox regression.

Results The study revealed that 18 out of 121 ICU patients (14.88%, 95% CI: 9.52-22.51%) died within 90 days post-discharge, while 36.36% achieved normal physical functional status. Factors associated with higher 90-day mortality included raised intracranial pressure (HR 1.92, 95% CI: 1.76–2.79, $p = 0.04$), acute kidney injury (HR 4.13, 95% CI: 2.16–7.89, $p < 0.01$), and renal replacement therapy (HR 3.34, 95% CI: 2.21–5.06, $p < 0.01$). The high mortality rate and the fact that nearly two-thirds of patients did not attain normal functional status 90 days post discharge underscores the need for enhanced post-ICU rehabilitation services.

Keywords Functional status, 90-day mortality, Intensive care unit, Low-income country, Karnofsky performance status

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Background

Critical illness in low-income countries(LICs) forms a significant component of the global disease burden [1], with patient populations relatively younger than those in high-income countries (HICs) [1, 2]. Despite this, critical illness in LICs is associated with higher mortality and morbidity than HICs, majorly because of limited resources [1, 3]. Research indicates that survivors of critical illness in LICs face elevated 30-90-day mortality rates; ranging from 6.2 to 57.3% [4–6]. Notably, no study in Sub-Saharan Africa has explored the long-term outcomes of ICU survivors.

Critical illnesses in LICs arise from a complex interplay of infectious diseases, such as HIV/AIDS, tuberculosis, and malaria, alongside non-communicable diseases (NCDs) like diabetes, hypertension, and trauma [7]. These conditions precipitate critical illness through various pathologies such as sepsis from untreated infections, acute respiratory distress syndrome (ARDS) and multi-organ failure stemming from the compounded effects of NCDs and infections [8]. These not only necessitate intensive care but also contribute to a challenging post-recovery phase. Approximately half of ICU survivors suffer lasting physical, cognitive or psychiatric complications with a post-ICU functional status often below premorbid status resulting in cognitive impairment and decline in performance of activities of daily living (ADLs) [9, 10].

Predictors of these outcomes include older age, comorbidities, APACHE II score, mechanical ventilation and other organ support, the severity of illness at ICU admission, pre-admission disability, and frailty [11–14]. Recognition of these complications is most apparent when patients attempt to resume normal community roles [15, 16]. The long-term burden of this reduced functional state increases healthcare costs to the individual, their families, the healthcare system and the community's Disability Adjusted Life Years(DALYs), impacting the nation's overall productivity [17].

Existing empirical data in our setting focuses on ICU and in-hospital mortality [2] but lacks information on mortality and functional outcomes beyond the hospital setting, where attending physicians play a minimal role. Additionally, there is a paucity of data quantifying the demand for post-ICU rehabilitative services and the long-term outcomes of survivors. Given the significant impact of physical functional impairment on independence, this study aims to determine physical functional status and 90-day post ICU discharge mortality rats, identifying associated factors. The findings will establish a baseline reference for advocating post-ICU care in low resource settings.

Methods

Study design and setting

We conducted a multicenter prospective cohort study to determine the 90-day mortality rate of ICU survivors from three tertiary hospital ICUs in Uganda and assessed their physical functional status at 90-days post-ICU discharge. We also determined the factors associated with 90-day mortality post-ICU discharge. The study was conducted for nine months (April 2022 - December 2022) in the ICUs of the Mulago, Nsambya, and Nakasero hospitals. These hospitals, located in Uganda's capital Kampala, were selected because they represent the three funding schemes for hospitals in Uganda i.e. Public, Private-not-for-profit and Private-for-profit, which impact quality of care provided by the critical care units. Mulago Hospital is Uganda's 1500-bed capacity teaching and national referral hospital. The hospital ICU has 16 beds, 10 of which are fully functional. Nsambya Hospital, a private not-for-profit Catholic-mission hospital has a 350-bed capacity with the ICU having 5 functional beds. Nakasero Hospital, a private for-profit hospital operates an ICU with 5 functional beds. The Ugandan healthcare system grapples with substantial challenges in infrastructure, staffing, and resources, particularly in critical care units, majority of which are concentrated in urban areas like Kampala and largely inaccessible to the average Ugandan [3].

Study population

Simple random sampling using a random number generator was used to select 121 patients aged $\geq$18 years, who were admitted as critically ill patients and discharged alive from Mulago, Nsambya, and Nakasero hospital ICU during the study period. We excluded patients who had spent less than 48 h in the ICU, refused consent, and those who had no telephone contact. The Kish Leslie formula was used to estimate the sample size at a 95% confidence interval with an error margin of 5% and adjustment for the accessible population for a three-month study period, taking into account a 15% attrition rate for potential loss to follow-up.

Data collection

Participants were enrolled in the study upon ICU discharge by trained research assistants, selecting those who met the inclusion criteria and obtaining informed consent from them or their next of kin. A pre-tested data collection tool gathered information on demographics, phone contacts, comorbidities, reasons for ICU admission, admission source, organ support, ICU complications, and other relevant clinical data. Electronic data collection was performed using ODK software, recording the discharge date for ease of follow-up up to day

90. Participants were contacted by telephone on days 30, 60, and 90 to assess vital and physical functional status, determined using the Karnofsky Performance Status (KPS) scale—a validated scoring system applicable via telephone [18]. For participants initially unreachable, follow-up attempts occurred every few days and weekly thereafter until the study's conclusion, with those remaining unreachable considered lost to follow-up. Acute kidney injury (AKI) was defined according to the KDIGO guidelines as any of the following: an increase in serum creatinine (SCr) by ≥0.3 mg/dl (≥26.5 µmol/l) within 48 h; an increase in SCr to ≥1.5 times baseline, known or presumed to have occurred within the prior 7 days; or a urine volume of <0.5 ml/kg/h for 6 h [19].

Data analysis

Continuous variables like age were summarized as median and interquartile range (IQR), while categorical variables were summarized as frequencies and percentages. Mortality was calculated as the total number of participants who died divided by the total number of participants followed up during the study period and expressed as a percentage. Kaplan Meier curves and log-rank test of equality were used to compare mortality across the ICUs. Cox regression analysis was used to determine factors associated with 90-day mortality. A variable with a p-value of <0.2 at bivariable analysis was considered for multivariable Cox regression model building. A p-value ≤ 0.05 was then regarded as significant. Interaction and confounding were assessed. The total score on the KPS scale determined the functional status with 100, indicating full activity with no symptoms, and 0, signifying death. Scores from 90−80% reflected normal activity with minor symptoms; 70−60% showed self-care ability but some work limitations; 50% indicated need for significant assistance and medical care; 40% indicated disabled needing special care; 30% severely disabled requiring non-urgent hospitalization; 20%, very ill needing urgent hospital care, and 10%, moribund with rapid disease progression [20].

Results

Two hundred forty-two patients were screened for eligibility, half (121) of whom were excluded from the study, aged less than 18, died before discharge, admitted for less than 48 h and refusal to consent. (Fig. 1). Eventually, one hundred twenty-one patients were enrolled in the study.

Baseline characteristics

The majority of study participants fell within the 20 to 44 age range, while individuals aged 45 and older constituted 23.14% of the entire cohort. Study participants were predominantly male, accounting for 57.85% of the participants. Pre-existing comorbidities were present in 47.93% of the participants before admission to the ICU. Among the study participants, 75 had a surgical-related illness. During their ICU stay, 10.74% received renal replacement therapy (RRT), and 22.31% received inotropic support. Mechanical ventilation was administered to 52.89% of participants, and the median length of stay (IQR) in the ICU was five days (3–11).

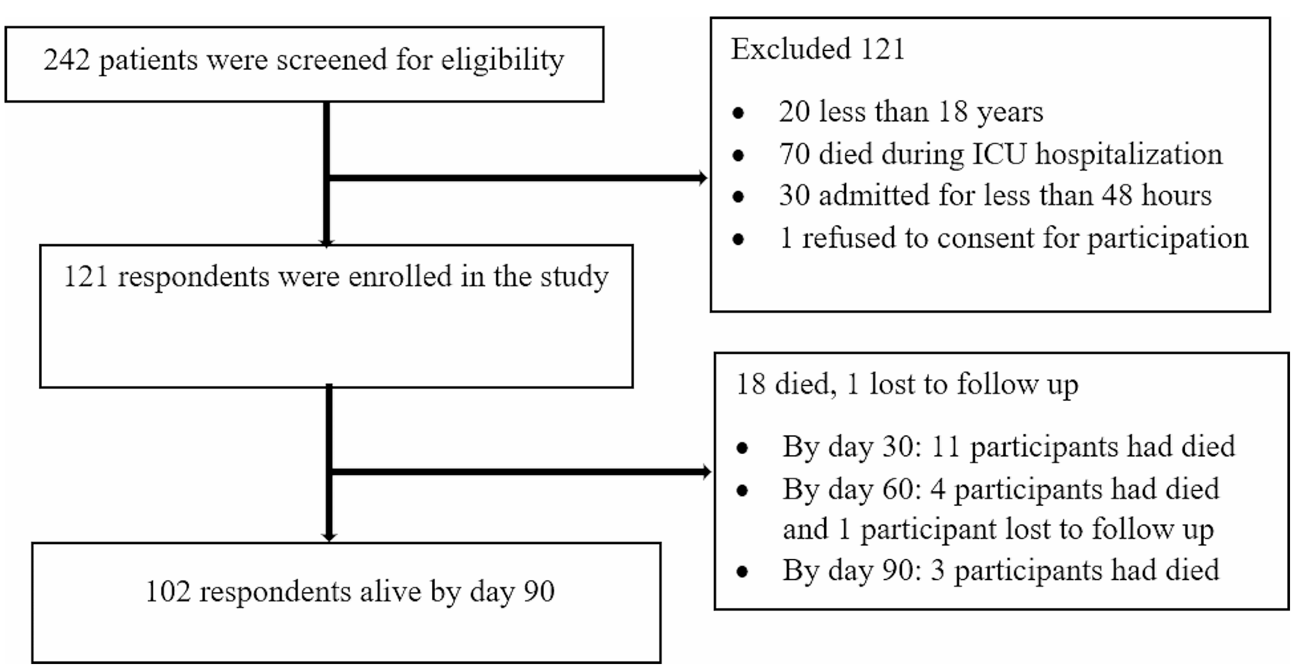

Fig. 1 Patient flow chart

Table 1 Demographic, clinical and treatment characteristics of 121 study participants

Characteristic	All *N* = 121 (%)	Survivors *N* = 103 (%)	Non-survivors *N* = 18 (%)	*P* value*
Age, years median (IQR)	45(30–63)	42 (29–61)	60 (39–66)	
≤ 19 years	5 (4.13)	5 (4.85)	0 (0)	0.44
20–44 years	54 (44.63)	49 (47.57)	5 (27.78)	
45–64 years	34 (28.10)	27 (26.21)	7 (38.89)	
≥ 65 years	28 (23.14)	22 (21.36)	6 (33.33)	
Sex				0.74
Male	70 (57.85)	58 (56.31)	12 (66.67)	
Hospital				0.09
Public	51 (42.15)	45 (43.69)	6 (33.33)	
Private for-profit	16 (15.53)	16 (15.53)	0 (0)	
Private Not-for-profit	54 (44.63)	42 (40.78)	12 (66.67)	
Marital status				0.17
Divorced/separated	5 (4.13)	4 (3.88)	1 (5.56)	
Married/Cohabiting	77 (63.64)	66 (64.08)	11 (61.11)	
Single/unmarried	30 (24.79)	25 (24.27)	5 (27.78)	
Widowed	9 (7.44)	8 (7.77)	1 (5.56)	
Comorbidities				0.01
Present	58 (47.93)	52 (50.49)	6 (33.33)	
Raised ICP				< 0.01
Yes	8 (6.61)	7(6.80)	1(5.56)	
TBI				0.03
Yes	37(30.58)	32(31.07)	5(27.78)	
PE with Hemodynamic Instability				0.09
Yes	4(3.31)	2(1.94)	2(11.11)	
AKI				0.04
Yes	18(14.88)	14(13.59)	4(22.22)	
Hypertensive emergency				0.03
Yes	14(11.57)	11(10.68)	3(16.67)	
RRT				0.17
Yes	13(10.74)	10(9.71)	3(16.67)	
Cardiac arrest				0.01
Yes	3(2.48)	1(0.97)	2(11.11)	
Inotropic/vasopressor support				0.24
Yes	27 (22.31)	24 (23.30)	3 (16.67)	
Non-Invasive Ventilation				0.08
Yes	65(53.72)	53(51.46)	12(66.67)	
Mechanical Ventilation				0.49
Yes	64(52.89)	51(49.51)	13(72.22)	
Length of hospital stay Median (IQR)	5 (3–11)	5(3–9)	7(4–18)	
Reasons for admission				
Postoperative admission	77(63.64)	68(66.02)	9(50.00)	0.79
Neurologic disorders	91(75.21)	76(73.79)	15(83.33)	0.12
Respiratory disorders	74(61.16)	60(58.25)	14(77.78)	0.31
Cardiovascular disorders	32(26.45)	28(27.18)	4(22.22)	0.13
GIT disorders	20(16.53)	19(18.45)	1(5.56)	0.91
Renal disorders	52(42.98)	40(38.83)	12(66.67)	0.48
Endocrine/ metabolic disorders	15(12.4)	14(13.59)	1(5.56)	0.58
Hematological Disorders	16(13.22)	14(13.59)	2(11.11)	0.20
Infectious	30(24.79)	22(21.36)	8(44.44)	0.47

ICP = intra cranial pressure; RRT = renal replacement therapy; AKI = acute kidney injury; TBI = traumatic brain injury; PE = pulmonary embolism P value: Obtained using Logrank test of equality of survival functions. *P values obtained using Logrank test

90-day mortality post ICU discharge

Following ICU discharge, 18 participants died, resulting in a mortality rate of 14.88% (95% CI: 9.52-22.51%). Among these, 6 were discharged from a public hospital ICU, while 12 were discharged from a private-not-for-profit hospital ICU resulting in mortality rates of 11.76% and 22.22% respectively. Over the 90 days, patients discharged from a private for-profit hospital exhibited lower mortality than those from public and private not-for-profit hospitals (Fig. 2). However, the difference in survival probability across all study ICUs was not statistically significant (p=0.09).

Ninety (90)-day functional status post ICU discharge

The median Karnofsky performance score at day 90 was 80.00%, a 20.00% increase from the median Karnofsky performance score at day 30 (Fig. 3).

More than a third (36.36%) of the study participants achieved a normal functional outcome, and atleast 18.18% required some level of assistance. (Fig. 4)

Factors associated with 90-day mortality at bivariate and multivariate analysis

At multivariate analysis, participants who had raised ICP were 1.9 times more likely to die at 90 days post-discharge compared to those who did not have (HR 1.92, CI 1.76–2.79). Participants who had AKI had a four-fold likelihood of dying compared to those who did not have AKI (HR 4.13, CI 2.16–7.89). Participants who had received RRT during their ICU stay had a threefold chance of dying post-ICU discharge compared to those who did not receive RRT (HR 3.34, CI 2.21–5.06). The bivariate and multivariate results are summarized in Table 2.

Discussion

This is the first prospective study in sub-Saharan Africa to study post-ICU long-term outcomes. We aimed to determine the 90-day mortality post-ICU discharge, ICU survivors' functional status, and factors associated with mortality at 90 days. This study was not motivated by the spate of COVID-19 ICU admissions, and we did not have any participants with COVID-19.

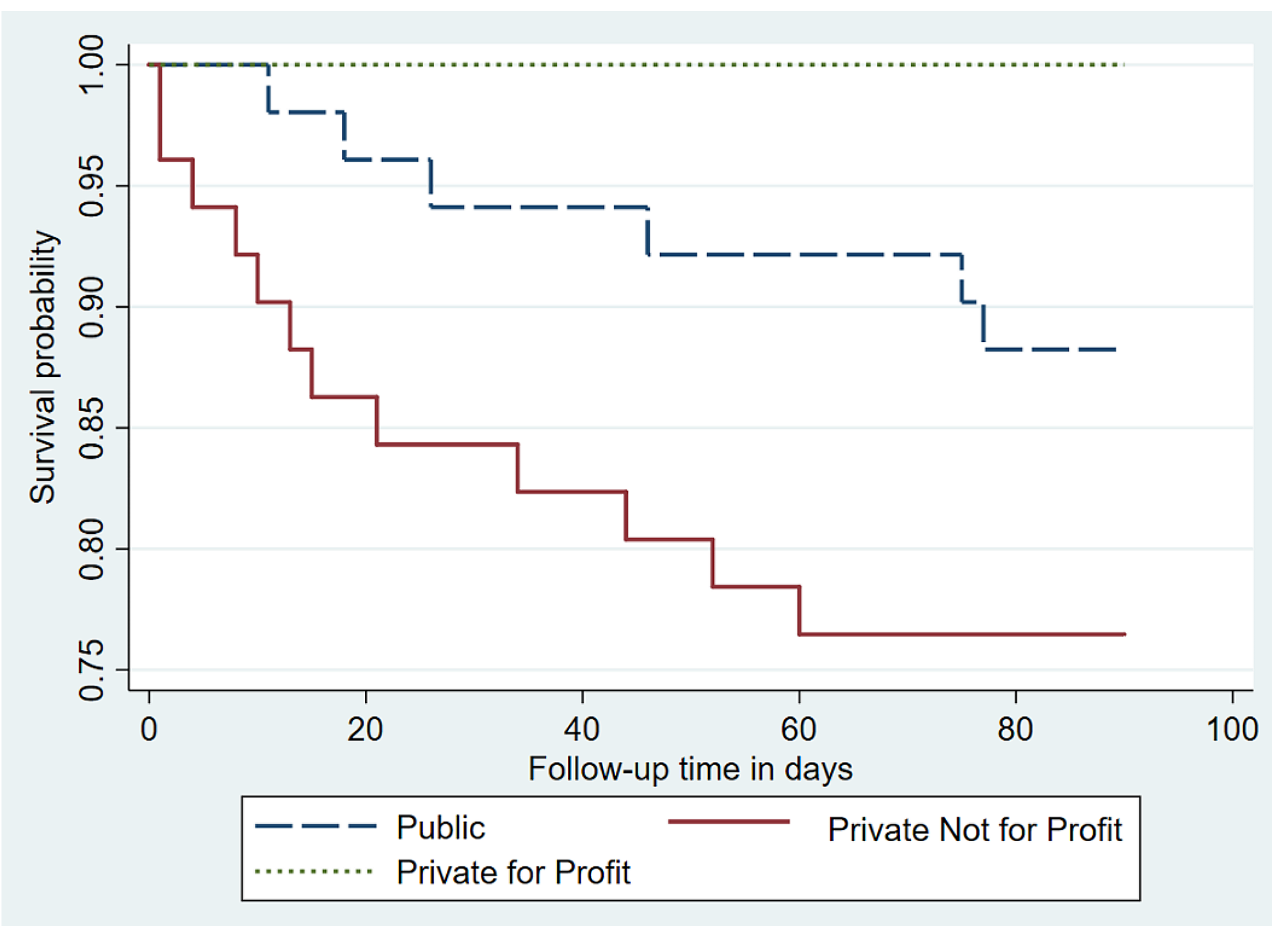

Fig. 2 90-day kaplan-meier survival estimates

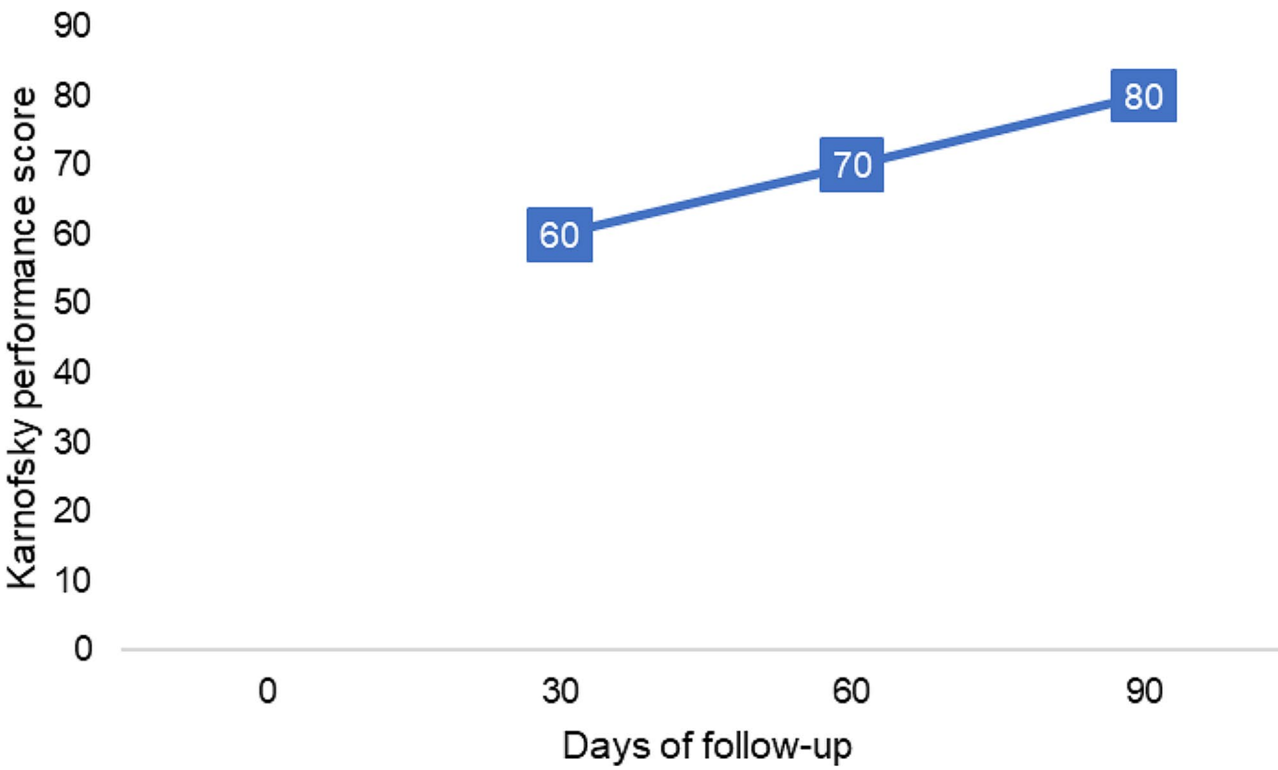

Fig. 3 Median karnofsky performance score at different time points

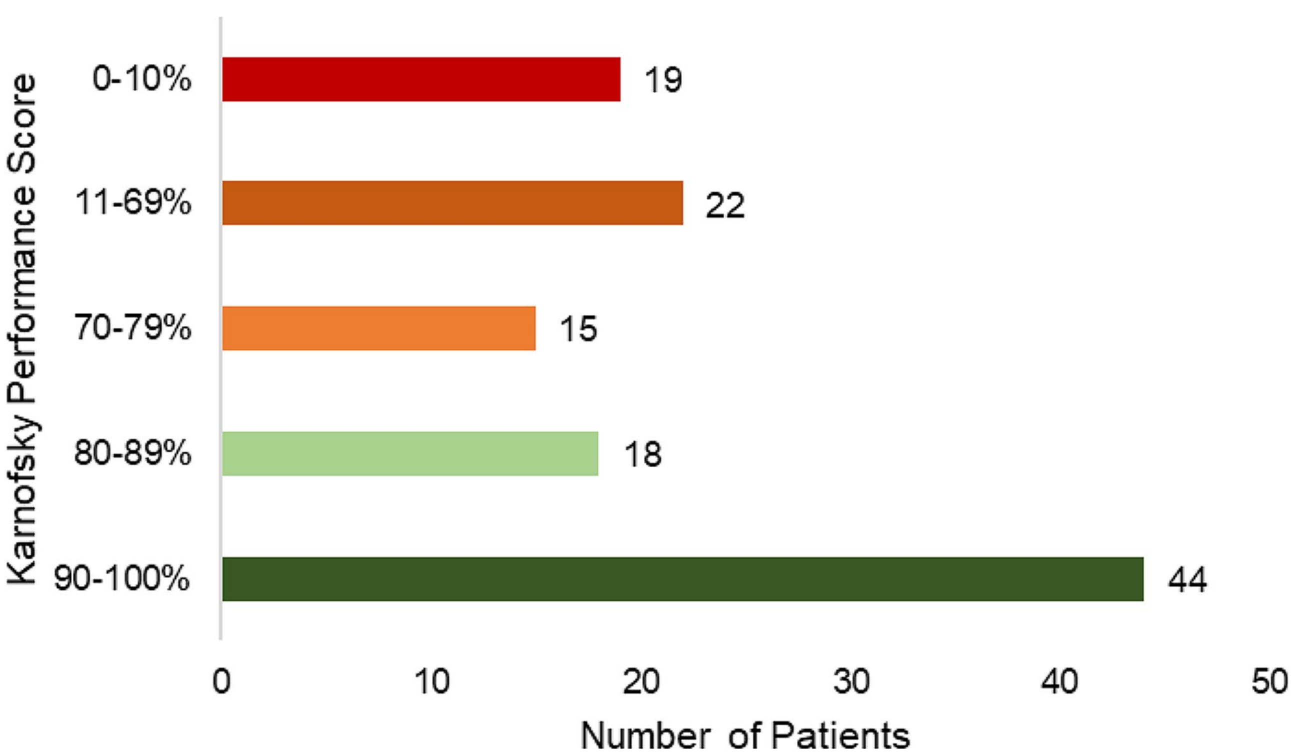

Fig. 4 Physical functional status of ICU survivors at 90 days following discharge from three tertiary hospital ICUs in Uganda

Table 2 Bivariable and multivariable analysis showing factors associated with 90-day mortality post-ICU discharge

Variable	Crude H.R.	p-value	Adj. H.R. (95% CI)	p-value
Hospital				
Private Not-for-profit	2.61	0.10	0.07 (0.00-7.21)	0.27
Private for-Profit	-	-	-	-
Public			1	
Marital status				
Married/Cohabiting	6.83	0.11	1.12 (0.00-378.57)	0.97
Divorced/Separated	-	-	-	-
Single/Unmarried	1.89	0.58	1	
Widowed	4.23	0.35		
Comorbidities				
Yes	0.21	0.02	0.06 (0.00-3.93)	0.19
No			1	
Raised ICP				
Yes	17.00	0.05	1.92 (1.76–2.79)	0.04
No			1	
TBI				
Yes	0.26	0.04	0.09 (0.00-4.60)	0.23
No			1	
PE with Hemodynamic Instability				
Yes	3.65	0.11	2.70 (0.21–34.78)	0.45
No			1	
AKI				
Yes	3.41	0.05	4.13 (2.16–7.89)	< 0.01
No			1	
Hypertensive Emergency				
Yes	4.04	0.05	2.50 (0.04-148.77)	0.66
No			1	
RRT				
Yes	2.42	0.19	3.34 (2.21–5.06)	< 0.01
No			1	
Non-Invasive Ventilation				
Yes	2.65	0.10	0.70 (0.06–8.38)	0.78
No			1	
Cardiac Arrest				
Yes	7.40	0.03	1	
No			1	

ICP = intra cranial pressure; RRT = renal replacement therapy; AKI = acute kidney injury; TBI = traumatic brain injury; PE = pulmonary embolism. H.R = Hazard ratio, CI = Confidence Interval

Our findings revealed a high post-ICU mortality rate of 14.88%, surpassing rates observed in other regions. Studies in Europe have reported a mortality rate ranging between 6.80–9.30% [4, 21]. The singular research focusing on post-ICU mortality in Africa occurred in South Africa. This study specifically examined 30-day mortality—a duration we regarded as short-term in comparison to studies conducted elsewhere that delved into post-ICU outcomes spanning three months to one year. The South African study, conducted prospectively, revealed a post-ICU mortality rate of approximately 6.20% [6].

The recorded mortality rates in our study appear to be higher than observed in other settings, potentially due to the constraints of our less-resourced ICUs, which impact patient care—a phenomenon supported by findings from Atumanya et al. in a Ugandan study detailing ICU capacity. This study indicated a scarcity of resources, with only 1.3 ICU beds per million population and a high nurse-to-patient ratio [3]. Additionally, the absence of a documented and established system for monitoring ICU survivors in our context may contribute to missed opportunities to prevent some avoidable deaths.

This study found that one in three ICU survivors achieved a normal functional outcome 90 days post-discharge, highlighting a notable contrast to studies conducted in developed countries. For example, a decade ago, Sacanella et al. followed patients for a year post-ICU discharge and found that maximum recovery was attained in the first three to six months following ICU discharge [22]. While Sacanella's study focused on patients from a medical ICU, our study encompassed both medical and surgical ICUs, potentially accounting for differences in functional outcomes. Most recently, in 2021, a prospective study in the United States demonstrated that 46% of ICU survivors at a tertiary hospital obtained a good functional recovery at one year post-discharge [23].

Conversely, Villa et al. established that there was moderate improvement in the functional outcome of ICU survivors at three months post-discharge in a study done in Spain, which is similar to our present study findings [24]. Moreover, some studies found a decline in functional status when patients were followed up after ICU discharge. For example, a prospective cohort done by Dietrich et al. in 2017 showed that ICU survivors had a poor functional status at three months post-discharge [25]. However Dietrich's study findings could be explained by the fact that they had a higher elderly population. In elderly persons, senescence, part of the natural ageing process, will most likely reduce functional reserve, hence a decrease in the functional status post-critical illness.

Notably, studies investigating functional outcomes post-critical illness have utilized varied instruments, such as the Karnofsky Performance Status scale (KPS) and Lawton-Instrumental Activities of Daily Living (IADL), to measure functional status, potentially explaining the difference in findings [26]. We chose to use the KPS in evaluating functional outcomes because of its easily defined categories, allowing for consistent measurement that could be carried out easily via telephone. The lack of a pre-ICU or baseline physical functional status (PFS) at ICU admission could have biased our conclusion in regard to the PFS. However, if pre-ICU PFS status were to be assessed, it would introduce a potential memory bias because of its retrospective nature [27].

The present study showed that participants who had AKI (denoted by; Serum Creatinine by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 h; or Serum Creatinine ≥1.5 times baseline; or Urine Volume < 0.5 ml/kg/hour for 6 h) had a four-fold likelihood of dying post-discharge, whereas those who had received RRT had a three-fold chance of mortality. We also found that those who had raised ICP were at increased risk of death. This increased risk possibly stems from lingering effects of these conditions persisting even after their departure from the ICU [4]. These patients therefore might require aggressive post ICU follow-up and rehabilitation.

The use of organ support, including mechanical ventilation and vasopressor/inotrope use, did not exhibit a significant association with mortality in our study. These results imply that, aside from renal replacement therapy (RRT), organ support likely has minimal residual impact on 90-day mortality following ICU discharge. This aligns with the findings of Atramont et al. in 2019, where no association was identified between long-term outcomes and organ support during the ICU stay [4]. On the contrary, at a university hospital in Korea, it was found that patients who had had mechanical ventilation had a 64.00% risk of death compared to those who did not at five years post-discharge [28]. The reason for the variance across these studies may be due to some methodological differences.

The association between Renal Replacement Therapy (RRT) and increased mortality observed in the study reflects significant insights into the challenges faced by post-ICU patients who have undergone RRT. From our data its unclear whether the patients with RRT were having renal recovery or dying from ESRD. However our findings are similar to studies done in other African countries [29, 30]. The need for RRT may indicate a more severe health state, which inherently carries a higher risk of mortality. RRT procedures like hemodialysis can lead to complications including infections, hemodynamic instability, and electrolyte imbalances, which can be fatal, especially in patients who are already critically ill [31].

We observed no association between the presence of comorbidities and post-discharge mortality—a surprising finding, particularly in light of previously published research that has firmly established such an association [21, 28, 32]. Patients with malignancies have been found that have 2.3 higher chances of death one year post-discharge from the ICU [12] just like patients with hematologic disease and solid tumours [28]. The difference between our findings and existing literature could be due to the small sample size in our study which may have affected the ability of the study to detect small effect sizes.

Additionally, our study did not find any association, between readmission and post-ICU mortality, despite the fact that readmission to the ICU has been shown to highly impact post-ICU mortality, with those being readmitted having higher odds of dying [12, 32]. The divergence of our findings from what is know again can be attributed to the small sample size of 7 readmitted patients in our study.

Strengths and limitations of the study

This is the first study in Uganda to study long-term post-ICU outcomes, providing crucial information that can be used to improve the quality of life of ICU survivors. The study was multicenter and had very minimal loss to follow-up.

The study had some limitations. We were unable to assess the severity of illness at ICU admission due to limited resources for calculating severity scores, such as APACHE II. Additionally, we did not record patients' baseline physical functional status (PFS) upon admission, despite its importance in influencing post-ICU outcomes. A major limitation was administering the Karnofsky Performance Scale (KPS) via telephone, which likely compromised assessment accuracy due to the absence of direct observation, reliance on patient self-reporting, and lack of visual cues. Furthermore, the use of second-hand reports from caregivers introduced reliability issues.

Conclusion

The study showed that post-ICU mortality at 90 days in a resource-limited setting was high at 14.88% and significant among those who had AKI, received RRT during their ICU stay and those who had raised ICP. Such patients could benefit from an established follow-up rehabilitation service and focused discharge program as they leave the ICU. Three months after ICU discharge, nearly two-thirds of patients did not attain normal functional status underscoring the need for post-ICU rehabilitation services. Larger studies and future research could focus on functional outcomes for longer periods in resource-limited settings.

Abbreviations

APACHE	Acute Physiologic and Chronic Health Evaluation
ADLs	Activities of Daily Living
AKI	Acute Kidney Injury
COVID	Corona Virus Disease
DALYs	Disability Adjusted Life Years
ESRD	End Stage Renal Disease
IADL	Instrumental Activities of Daily Living
HICs	High Income Countries
ICP	Intracranial Pressure
ICU	Intensive Care Unit
IQR	Interquartile Range
KDIGO	Kidney Disease: Improving Global Outcomes
KPS	Karnofsky Performance Status
LICs	Low Income Countries
NCDs	Non-communicable Diseases
ODK	Open Data Toolkit
PFS	Physical Functional Status
PFT	Private for Profit
PNFP	Private Not For Profit
RRT	Renal Replacement Therapy
SOMREC	School of Medicine Research Ethics Committee
TBI	Traumatic Brain Injury

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Author contributions
H.W.M conceived the study idea, designed the study, applied for the partial funding of the research and wrote the first draft of the manuscript supervised by C.S, T.S.L, A.W and P.K.A. C.S contributed to the study design. N.M and A.P conducted the data analysis and supported data collection. Interpretation was done by H.W.M, C.S, T.S.L, A.W and P.K.A. All authors contributed to the development of the manuscript, read and approved the final manuscript.

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Data availability
The original dataset used and or analyzed during the study is available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Permission to carry out the study was obtained from the Makerere School of Medicine Research and Ethics Committee (SOMREC), approval reference number Mak-SOMREC-2022-289. We also sought permission from Uganda National Council of Science and Technology (UNCST), approval reference number HS2143ES. Administrative clearance was obtained from the Mulago Hospital Ethics Committee, Nsambya Hospital Research Ethics Board and Nakasero Hospital Research Ethics Committee. Informed consent was obtained from each patient. If the patient could not consent at discharge, it was obtained from the next of kin. This was because some of the patients discharged were incapacitated with reduced level of Glasgow coma scale or consciousness hence impeding their participation in the consenting process. The study team observed the COVID-19 standard operating procedures while conducting this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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