ICU Memories and Patient Outcomes in a Low Middle–Income Country: A Longitudinal Cohort Study

Swagata Tripathy, MD, DNB, IDCC, EDIC[1]

Nilamadhab Kar, MD, DPM, DNB, MRCPsych[2]

Swati P. Acharya, BA[3]

Santosh Kumar Singh, MD, PDF[2]

OBJECTIVES: To study memories of ICU following discharge, their associations, and impact on mental health and quality of life in a low- and middle-income country.

DESIGN: Prospective observational cohort; data on memories (pain, fear, nightmare, factual), clinical and demographic variables, anxiety-depression, posttraumatic stress symptoms, and quality of life were collected 0, 7, 14, 30, 90, and 180 days post discharge. Home visits for assessment minimized loss to follow-up. Linear mixed-models and regression analyses were used to estimate adjusted effects of memories controlling for age, sex, time, and severity of illness.

SETTING: Twenty-five bedded ICU of a tertiary care center in East India.

PATIENTS: Adult ICU survivors between January 2017 and July 2018 able to communicate their memories.

INTERVENTIONS: Not applicable.

MEASUREMENTS AND MAIN RESULTS: Final sample consisted of 322 patients who completed 180 days follow-up. Pain, fear, factual, and nightmare memories dropped from 85%, 56%, 55%, and 45% at discharge to less than or equal to 5% at 180 days. Patients with gaps in ICU memory had worse anxiety-depression, posttraumatic stress symptoms, and quality of life at all follow-up points. Sedation (odds ratio, 0.54; CI, 0.4–0.7), steroids (odds ratio, 0.47; CI, 0.3–0.8), benzodiazepines (odds ratio, 1.74; CI, 1–3.04), and mechanical ventilation (odds ratio, 0.43; CI, 0.2–0.8) were independently associated with gaps in memory. Non-ICU factor such as substance addiction (odds ratio, 5.38; CI, 2–14) was associated with memories affecting mental health and quality of life.

CONCLUSIONS: Gaps in memory and various memory types were common after ICU admission, whose prevalence waned over time. Compared with nightmares and fearful memories, gaps in memories were most strongly associated with poor mental health and quality of life. Identifying patients with gaps in memories might be an objective way of planning interventions to improve their long-term outcomes.

KEY WORDS: anxiety; depression; ICU memories; India; post-ICU psychologic stress; quality of life

Postintensive care syndrome (PICS) is considered a significant component of patient-reported quality of life (QOL), a focus of modern critical care (1). Memories of ICU are linked with post-ICU mental health (MH) (2). Most research on ICU-related posttraumatic stress symptoms (PTSS) and

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post-ICU MH burden comes from studies in developed countries (3, 4). Previous studies have found different types of memories associated with anxiety or stress symptoms (5–7). Memories of nightmares, delusion, and gaps in memories have been associated with worse QOL and PICS after discharge (8, 9). The link between ICU memories and QOL or MH outcomes is far from established (10–13), with limited information on the patient (demographic and clinical) and ICU factors affecting them (2, 14).

We postulated that memories, their course, causation, and effect might differ in patients from dissimilar cultural and socioeconomic backgrounds of low- and middle-income countries (LMICs) where the conventional high-income country (HIC) resource-intensive ICUs with extensive monitoring, equipment, and large numbers of highly trained staff are less common (15). Our specific objectives were to study: 1) the course of ICU-related memories over 6 months, 2) how memory types and gaps affect patients' QOL and MH, and 3) which patient and ICU factors affect memories.

MATERIALS AND METHODS

Data Source

It was a longitudinal/prospective, observational study that assessed patients at multiple time points following ICU discharge, with recruitments from January 2017 to July 2018. Data were collected alongside a study of critical care-associated PTSS and anxiety-depression (16). The study site is a 25-bedded ICU (8 surgical and 17 medical beds) in a 600 bedded, government-funded, tertiary-level teaching institute in Odisha, India. The ICU is covered by one trained intensivist on rota each month, helped by one postgraduate critical care trainee during the day and an undergraduate anesthesia trainee at night. The nurse:patient ratio varies, usually 1:2 for ventilated and 1:3–4 for nonventilated patients. Ancillary support of respiratory technician, nutritionist, pharmacist, and high-end equipment for renal replacement therapy and extracorporeal membrane oxygenation is not available. Although evidence-based ICU protocols are in place, the implementation is less than ideal. Analgesia is preferentially given in intermittent dosing, and infusion of generic dexmedetomidine (comparatively inexpensive in India and government-funded at our center) is preferred over propofol infusion for sedation.

Consenting adult ICU survivors with a stay of more than 24 hours was included (**Fig. 1**). Death or lack of meaningful communication at any follow-up resulted in exclusion. A "meaningful communication" meant being able to convey one's viewpoint: verbally, by writing, or by gestures.

Assessments included a face-to-face interview at ICU discharge and day 7 (or hospital discharge) and around 14, 30, 90, and 180 days, telephonically or face-to-face during hospital visit by a dedicated clinical psychologist. Where telephonic responses were inadequate, patients missed hospital appointments, or inexplicable deviations occurred from previous scores, home visits were arranged (around 100). This allowed for near-complete data collection and minimal dropout (four/389 patients).

Demographic and Clinical Data

Sociodemographic variables—age, sex, education, employment status, and having children less than 18 years old; clinical variables—diagnosis, mental illness or substance abuse/addiction, and traumatic experiences (life-threatening accident, physical/sexual abuse, or disaster)—; and level of social support were recorded. ICU data included Acute Physiology and Chronic Health Evaluation (APACHE)–II (17), Sequential Organ Failure Assessment (18), Richmond Agitation and Sedation Scale (RASS) scores (19), Visual Analogue Pain Assessment scores, duration of mechanical ventilation, steroid, sedatives, delirium (treated with antipsychotics), and vasopressors (type, dose, and indication).

Assessment of Memory. Memories were classified as "nightmare," "pain," "fear or panic," and "factual" like previous studies (20, 21). The questions were presented in a self-rated format for frequency, ranging from 0 to 2 (never, sometimes, and often) at the follow-up interviews.

The ICU memory tool (ICUMT) was administered between 90 and 100 days of discharge from the ICU (21). It consists of a checklist of memories in three domains: ICU environment (family, alarms, tubes), feelings (pain, agitation, confusion), delusions (dreams, hallucinations), and questions to assess recall of the hospitalization, reexperiencing and discussing the ICU experience with others. "Gaps' were noted when the patient reported ICU memory as hazy or struggled to remember some ICU experience aspects. In contrast, complete memory was considered when there was no difficulty remembering the ICU stay (a subjective feeling of complete recall).

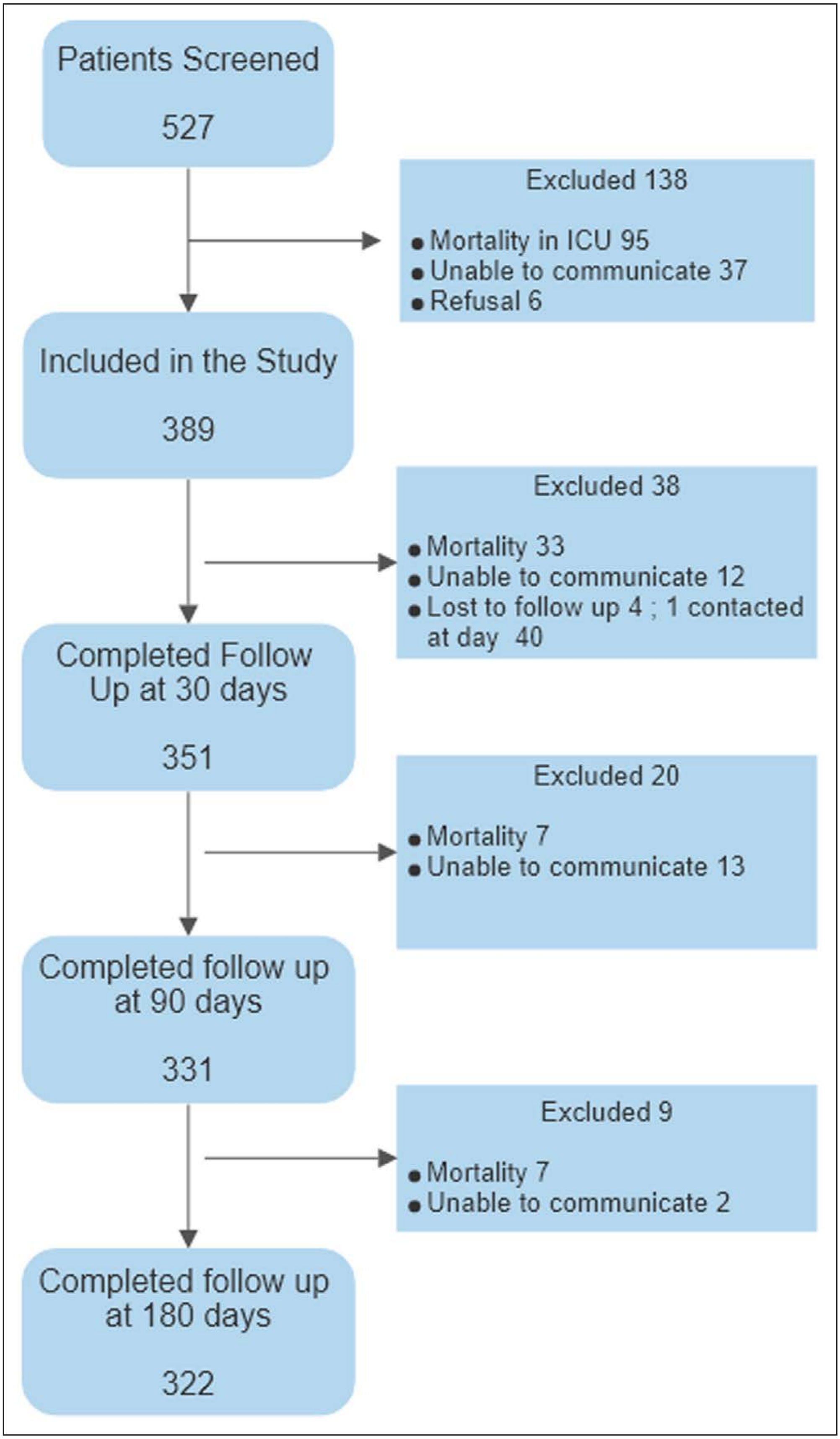

Figure 1. Diagram of patient recruitment and follow-up.

Assessment of MH Outcomes and QOL

We used the Hospital Anxiety and Depression Scale (HADS) (22) for assessing anxiety-depression, Impact of Events revised tool (IES-r) (23) for PTSS, and European QOL 5 Dimensions (EQ5D) 3 levels (24) for QOL at each follow-up point, that is, 0, 7, 14, 30, 90, and 180 days. The HADS has 14 questions for assessing anxiety-depression separately, with a cut off score of greater than 7 each. The IES-r has 22 questions with intrusion, avoidance, hyperarousal subscales, and a cut off score of greater than 30.

All these questionnaires and instruments have been validated in ICU patients (25). We have validated the EQ5D in the local language (Odia) (26); a bilingual professional back-translated other tools according to the Brislin model (27). The final versions used were pilot tested on a consenting patient discharged earlier from the ICU and modified as needed.

Data Analysis and Statistics

Data are expressed as mean ± SD or the median and interquartile range. We used the Students' *t* test for normally distributed continuous variables, chi-square statistics for categorical data, and Mann-Whitney *U* tests for nonparametric data.

The type, frequency, time-course, and factors affecting memories (nightmares, pain, fear, and factual) were analyzed over 6 months. We used longitudinal mixed-effects regression analyses recommended for repeated measures over time (28) for memory predictors. The maximum-likelihood method fixed and random effects accounted for changes over time. The model with the least Akaike Information Criterion was selected. Multivariate regression (ICUMT data) generated the factors associated with and MH effects of memories and gaps. Factors were chosen if hypothesized or significant ($p < 0.1$) on univariate analysis. A sensitivity analysis was done for the subgroup of ventilated patients.

The sample size was based on previous studies (2, 29) for a 90% power and type 1 error of 0.05 to detect a 12% difference in EQ5D scores between patients with or without gaps in ICU memory. Home visits resulted in a high response rate (98%). For the few missing or answered "I cannot say," we used multiple imputations. SPSS (Version 22.0; SPSS, Chicago, IL) was used for analyses (except R Statistical Software v3.6.1 [R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/] for linear mixed-models); *p* values of less than 0.05 was considered statistically significant.

Ethics and Governance

The study was reviewed and approved by the Institutional ethics committee of All India Institute of Medical Sciences (IEC/AIIMS/APP/2017/3) with sponsorship from Indian Council of Medical Research. It was registered at Clinical-Trials-Registry-India (CTRI/2017/07/008959). Written informed consent was obtained from all participants or next of kin.

RESULTS

Of 527 patients screened, 389 were recruited, 67 excluded, and 322 (82.8%) completed 6 months of follow-up (Fig. 1). The mean age ± SD was 48 ± 16 years. More than half were males (60%), unemployed or retired (62%), and educated beyond primary school (81%). Sample characteristics are given in **Table 1**. Patient categories were post surgery (36%, 11% elective), medical (31%), neurologic (21%), and trauma (11%). Substance use was reported by 33.5%, mostly (15.8%) betel quid (arecoline), common in the region, and alcohol (8.4%). The mean APACHE score was 9.4 ± 4.6, and the median duration of ICU stay was 3 days (range, 2–28 d). Around half (52%) of patients were ventilated for greater than 48 hours, 10% for greater than 7 days. Almost 45% received at least one stress dose of steroids (150 mg hydrocortisone in three doses over 24 hr). Mean pain and sedation scores were 2.3 ± 1.1 and –0.4 ± 0.9.

Memories of the ICU

One third of the patients reported gaps in ICU memory. Table 1 compares these two groups. Changes over time and memory examples appear in **Figure 2** and **Supplement 1** (http://links.lww.com/CCM/G389), respectively.

Effect of Gaps and Types of Memory on MH and QOL

Median QOL, PTSS, and Anxiety-Depression Scores were better in patients without gaps in memory (**Table 2**). The significant association was retained when adjusted for baseline factors: age, gender, and severity of illness in the ICU ($p < 0.05$).

At 3 months, the mean Anxiety-Depression Score was more (worse) in patients with memories of nightmares and frightening memories: 3.15 versus 2.09 ($p = 0.00$) and 2.72 versus 2.09 ($p = 0.00$), respectively. QOL scores (0.77 vs 0.86; $p = 0.01$) were less (worse) in patients with frightening memories.

Factors Affecting Gaps and Types of Memories

Factors affecting both gaps and types of ICU memory are given in **Table 3**. After correcting baseline factors, including the severity of illness, mechanical ventilation, steroids, a higher score on RASS (lighter sedation or agitation), and benzodiazepines, were associated with a greater risk of memory gaps. In the sensitivity analysis for ventilated patients, steroids (odds ratio [OR], 2.3, CI, 1.1–5.1), higher sedation score (OR, 1.8, CI, 1.2–2.7), and benzodiazepines (OR, 1.1; CI, 1.0–1.2) retained their significant association age, and substance addiction among patient factors and ICU factors such as benzodiazepines, mechanical ventilation, sedation scores, and steroids affected different memory domains in our cohort. The results corrected for baseline factors are shown in Table 3.

TABLE 1.
Clinical and Demographic Characteristics of 331 Patients Enrolled in the Study by ICU Memories Status

Variables	Total	Memories of ICU stay: Gaps in Memory (n = 110; 33%)	Memories of ICU stay: Complete Memory (n = 221; 67%)	p[a]
Age (yr), mean ± SD	48 ± 16	45 ± 17	49 ± 16	0.04[a]
Sex, n (%)				
Female	134(40)	43 (32.1)	91 (67.9)	0.54
Male	197 (60)	66 (33.5)	129 (65.4)	
Employment, n (%)				
Unemployed	204 (62)	71 (34.8)	133 (65.1)	0.4
Employed	127 (38)	39 (30.7)	88 (69.3)	
Education, n (%)				
No formal education	63 (19)	17 (27.0)	46(73.0)	0.08[a]
Primary education	247 (75)	83 (33.6)	164 (66.4)	
Secondary school and above	21 (6)	10 (47.6)	11 (52.4)	
Children under 18 yr, n (%)	81 (25)	32 (39.5)	49 (60.5)	0.17
No children < 18	250 (75)	78 (31.2)	172 (68.8)	
Substance abuse, n (%)				0.012[a]
No	223 (69)	64 (28.7)	159 (71.3)	
Yes	108 (31)	46 (42.6)	62 (57.4)	
Charlson's comorbidity index, mean (± SD)	1.27 (± 1.5)	1.05 (± 1.3)	1.4 (± 1.6)	0.06
Length of stay ICU, median (IQR)	3 (2–28)	4 (2–24)	3 (2–28)	0.04[a]
Acute Physiology and Chronic Health Evaluation II, median (IQR)	9 (1–27)	9 (1–28)	8 (1–25)	0.31
Sequential Organ Dysfunction Assessment score, median (IQR)	2 (0–21)	2.5 (0–14)	2 (0–21)	0.03[a]
Mechanical ventilation, n (%)				0.001[a]
None	158 (47.7)	37 (23.4)	121 (76.5)	
48 hr to 1 wk	140 (42.3)	62 (44.3)	78 (55.7)	
> 1 wk	33 (10)	11 (33.3)	22 (66.6)	
Pain score, mean ± SD	2.3 ±1.1	2.3 ± 1.2	2.3 ± 1.1	0.9
Sedation score, mean ± SD	−0.4 ± 0.9	−0.3 ± 0.9	−0.5 ± 0.8	0.06

(*Continued*)

TABLE 1. (*Continued*).
Clinical and Demographic Characteristics of 331 Patients Enrolled in the Study by ICU Memories Status

Variables	Total	Memories of ICU stay: Gaps in Memory ($n = 110$; 33%)	Memories of ICU stay: Complete Memory ($n = 221$; 67%)	p[a]
Administered steroids, *n* (%)				0.00[a]
No	184 (55.6)	45 (24.5)	139 (75.5)	
Yes	147 (44.4)	65 (45.1)	79 (54.9)	
Delirium, *n* (%)				0.29
No	259 (78.2)	88 (34.0)	171 (66.0)	
Yes	72 (21.7)	22 (30.5)	50 (69.4)	
Social support, *n* (%)				0.71
High	102 (30.8)	31 (30.4)	71 (69.6)	
Medium	163 (49.2)	55 (33.7)	108 (66.3)	
Low	66 (19.9)	24 (36.4)	42 (63.6)	

IQR = interquartile range.
[a]Mann-Whitney *U* test was used for continuous variables and χ^2 for categorical ones.
All the percentages are calculated row-wise.

DISCUSSION

In this prospective study in India, we found that ICU memories' frequency decreased over time. Gaps in memory were associated with worse QOL and MH outcomes. Different ICU and patient factors were associated with gaps and types of memories. Patient profiles such as age, comorbidities, type of substance use, case mix, and cultural beliefs related to critical illnesses are different in ICUs of HICs and LMICs. Betel nut use is widespread (30). Severe competition for ICU beds, relatively low staffing, overcrowded, and ill-resourced areas from which patients arrive or return may influence experiences and memories (31).

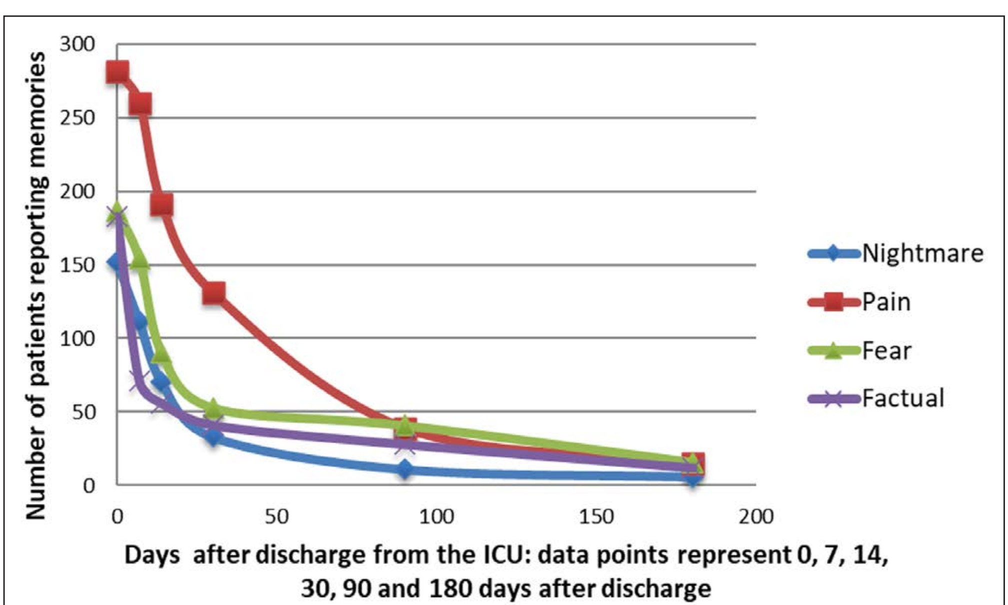

Figure 2. Change in ICU memory types over time.

ICU Memories

Various ICU-related memories were reported

TABLE 2.
Difference in Median Quality of Life, Posttraumatic Stress Symptoms, and Anxiety/Depression Scores at Hospital Discharge, 1 Month, And 3 Months After ICU Discharge Between Patients Who Have Complete Memory of ICU Stay Versus Those Who Do Not (Gaps in Memory)

	Quality of Life			Posttraumatic Stress Symptoms			Anxiety/Depression		
Memory	At Discharge	1 mo	3 mo	At Discharge	1 mo	3 mo	At Discharge	1 mo	3 mo
Complete memory	0.24	0.74	1.0	6	2	0	9	3	2
Gaps in memory	0.18[a]	0.68[a]	0.77[a]	9[a]	3[a]	1[b]	10[b]	4[a]	3[a]

[a] $p < 0.001$.
[b] $p < 0.05$.

by considerable proportions (range for types of memories 46–85%) of patients, which decreased to 2–5% by 6 months. Previous studies have reported that the memories of feelings (pain and fear) predominated at discharge and decreased sharply with time (7, 32), but a few patients could recall the pain intensity after a period of discharge (4). Future studies may be pertinent to account for this time decay by appropriate mixed model statistics.

Factors Affecting Memories and Gaps

Patient Factors. Studies show variable factors associated with different memory domains (9, 20, 32–34). Differences may be due to study design, patient sampling, and interview techniques (33). Cultural differences in memory interpretations may lead to variable classification; for example, memories of the "breathing tube," alarms, suctioning, injections, changes in position, and physiotherapy more often classified as painful or frightful in previous studies were classified "factual" by our cohort. We found that factual memories decreased with increasing age, similar to the study by Burry et al (7). Addiction (infrequently commented on in previous studies) was associated with nightmare memories demonstrating a need to explore the role of substances and addictive drugs in the context of long-term outcomes of ICU memories. Interestingly, contrary to our hypothesis, most other patient factors were not associated with memories; having young children and being employed at the time of admission lost their association on correcting for other factors.

ICU Factors. A minimum dose of 150 mg hydrocortisone in divided doses over 24 hours (to prevent postextubation stridor) in our cohort was associated with higher risk of fearful memories akin to a single dose of 25 mg of cortisone previously (35). Variably associated with delusional memories on the one hand and improved MH outcomes on the other (36–38), the dichotomous association of steroids warrants further research. Patients are referred from other centers on steroids and might be discharged home with oral steroids: the effect of cumulative dose or types of steroids may yield different results than ours. The effects of benzodiazepines, sedation, and mechanical ventilation on different memory types have been observed in previous studies (7, 9, 39, 40).

Gaps in Memory. Among the factors affecting gaps in memory found in our study, ventilation, benzodiazepines, and steroids have not been explored as much as sedation. The effect of sedation depth on completeness of recall of ICU stay is controversial. One study found that deeply sedated patients had significant trouble remembering important parts of their ICU experience (40), but other studies reported no effect of the type or depth of sedation (4, 7). The effect of intermittent dosing of opioid analgesics and dexmedetomidine sedation in our cohort may have different effects than continuous sedation or sedation with vacation: considerable differences exist in sedation practices between ICUs internationally (41) and also on how the depth of sedation is analyzed in studies (time spent in deep sedation or coma [7] vs mean sedation over ICU stay).

TABLE 3.
Factors Contributing to ICU Memories

Memory	Variables	OR	95% CI of OR	*p*
Gaps in memories[a]				
	Age	0.99	0.97–1.00	0.16
	Education			0.61
	No formal education	1.59	0.78–3.24	0.19
	Primary education	1.79	0.51–6.27	0.36
	Secondary school and above	0.001	0.01–0.003	0.99
	Severity of illness	0.97	0.91–1.03	0.41
	Addiction	0.88	0.51–1.53	0.67
	Mechanical ventilation	2.46	1.35–4.46	< 0.01
	Midazolam equivalent mg	1.09	1.01–1.18	0.03
	Steroids	2.08	1.17–3.7	0.01
	Sedation score	1.81	1.28–2.44	< 0.01
	Delirium	0.96	0.91–3.46	0.87
Type of ICU memory[b]				
Nightmares	Addiction	4.87	1.87–12.67	0.001
	Midazolam equivalent mg	1.16	1.04–1.29	0.008
Fear	Midazolam equivalent mg	1.1	1.03–1.18	0.004
	Steroids	2.51	1.31–4.81	0.006
Pain	Sedation score[c]	1.7	1.08–2.68	0.02
Factual memories	Age	0.93	0.89–0.97	0.001
	Mechanical ventilation	5.32	1.63–13.54	0.006
	Midazolam equivalent mg/d	1.16	1.03–1.3	0.02

OR = odds ratio.

[a]Factors in the model: age, education, severity of illness (Acute Physiology and Chronic Health Evaluation II score), addiction, mechanical ventilation, benzodiazepines, steroids, and sedation score (Richmond Agitation Sedation Score), delirium.

[b]Linear mixed model statistics for patient and ICU factors associated with ICU memories over repeated measurements over time. Time was associated with a significant drop in memory, in all the memory domains.

[c]A higher sedation score signifies greater restlessness and agitation.

Factors in the model: age, gender, education, marital status, employment, addiction, severity of illness, ICU length of stay, delirium, sedation level, midazolam equivalents per day, steroids stress dose, mechanical ventilation, time.

Influence on Patient Outcomes

One third of the patients in our study reported gaps in memory, which were consistently associated with lower QOL, higher PTSS, and higher anxiety and depression at discharge, 1 and 3 months of follow-up. Studies from HICs have similarly reported worse MH (PTSS, anxiety, and depression) and QOL among patients reporting memory gaps (2, 7), memories of nightmares, and fearful memories (3–7), which are rated important domains affecting perceived QOL after ICU discharge (42). We did not find PTSS to be affected significantly by any memory domain; it appears that our study was not powered to detect this association.

ICU factors affecting different types of memories may be limitedly modifiable. Identifying gaps in ICU memories may provide a suitable start point for identifying patients at risk of worse outcomes and designing interventions; ICU diaries (35) and audiovisual aids (43) are some of the efforts in that direction.

Strengths

We believe that this is the first such prospective study from an LMIC. It has an adequate sample size, more than many previous studies. Demographic and clinical factors are explored in greater depth. The study included all eligible adult patients at the entry into a mixed surgical-medical ICU, ensuring a representative sample and minimizing selection bias. We used standardized and validated instruments. A clinical psychologist performed all the assessments at follow-ups and home visits, enabling greater compliance of participants, high response rates, low dropout, and ameliorating any interrater issues.

Limitations

The day 1 Severity Of Illness score is low in our cohort: probably because of a strict triage by the ICU-outreach team, the nature of disease, and a young population (44). Although adjusted for, results may not apply to patients with higher acuity. Pre-ICU QOL was not available, as in the previous studies. Only two patients reported prior mental illness; the lower figure could be due to greater stigma in the LMICs, among other factors (45). This study may have missed hypoactive delirium by not using a validated tool for delirium assessment. Memory gaps were patient reported; the subjective report of "complete memory" might differ from objective "completeness" measured through a validated instrument.

CONCLUSIONS

The focus on post-ICU QOL and PICS is increasing in recent times. We believe our results are the first to emerge from an LMIC and among few to report the effects of patient factors on post-ICU memories. Preadmission substance use, benzodiazepines, and steroids affected fear and nightmare memories and worsened MH and QOL. Gaps in memories were associated with (modifiable) ICU factors such as sedation, steroids, benzodiazepines, and mechanical ventilation after correcting other factors. Our results might encourage further research to explore interventions that address memory gaps and use preidentified factors to recognize at-risk ICU patients.

1 Department of Anesthesia and Critical Care, AIIMS Bhubaneswar, Odisha, India.

2 Department of Psychiatry, Black County Healthcare NHS Foundation Trust, Wolverhampton, United Kingdom.

3 Department of Psychiatry, AIIMS Bhubaneswar, Odisha, India.

Current address for Dr. Singh: Hematology ICU, IMS & SUM Hospital Bhubaneswar, Bhubaneswar, Odisha, India.

This work was performed at All India Institute of Medical Sciences, Bhubaneswar, India.

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

Ethics approval given by the Institute Ethics Committee of AIIMS Bhubaneswar.

Written consents were taken from all participants or next of kin (https://aiimsbhubaneswar.nic.in/ethicsCommittee.aspx#).
Consent for publication is present.

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Address requests for reprints to: Swagata Tripathy, MD, DNB, IDCC, EDIC, Additional Professor and in-charge ICU, Department of Anesthesia and Critical Care, AIIMS Bhubaneswar, Room 406, Academic Block, Odisha, India. E-mail: tripathyswagata@gmail.com

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