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Meta-analysis on Subsyndromal Delirium in ICU

Moath Mohammad Alothman[1] , Haitham Abdullah Alnahedh[2] , Saleh Khader Alghamdi[3] , Abdulrahman Khalid Aljarallah Intern [4] , Ghazi Abdulmalik ashoor[5] , Hebah Adel Mansour [6] , Ramy Fahad Alshawan[7] , Khalid Mohammed A Asiri[8] , Muteb Lafi Alenazi [9] , Salem Abshan M Alshehri [10], Khalid Nasser M Sinnah[11] , Aisha Esam taiyeb[12]

1- PHC at Dammam City, 2- Al Iman General Hospital, 3- King Saud Medical City , 4- King Abdulaziz University , 5- Alfaisal University , 6- Jeddah Eye Hospital, King Abdulaziz University , 7- Al Amal Hospital , 8- Muhayel General Hospital , 9- Arar Central Hospital , 10- Prince Abdulaziz Bin Musaed Hospital- Arar , 11- ACH (Aseer Central Hospital) , 12- King Abdullah Complex Hospital

ABSTRACT

Background: Subsyndromal delirium (SSD) is a frequent condition and has been commonly described as an intermediate stage between delirium and normal cognition. However, the true frequency of SSD and its impact on clinically relevant outcomes in the intensive care unit (ICU) remains unclear.

Aim of the Study: To evaluate the significance of SSD on adverse clinical outcomes especially mortality and length of hospital stay.

Methods: A systematic search was performed in the scientific database particularly MEDLINE (2000–2017), EMBASE (2000– 2017), Cochrane Central Register of Controlled Trials, CINAHL (2000–2017), Google Scholar, and individual journals to identify publications that evaluated SSD in ICU patients.

Results: The search yielded five studies involving 2453 patients. SSD was detected in 849 patients (34.6%). Three studies evaluated only surgical patients. Three studies used the Intensive Care Delirium Screening Checklist (ICDSC) and two used the Confusion Assessment Method (CAM) score to diagnose SSD. The meta-analysis showed an increased hospital length of stay (LOS) in SSD patients (0.29 (95% CI 0.11–0.48), $p = 0.002$; $I^2 = 33\%$). Hospital mortality was described in two studies but it was not significant (hazard ratio 0.93 (0.58–1.43), $p = 0.88$ and (4 (1.0-6.9) vs 9 (3.6-20.4), $p = 0.05$). The use of antipsychotics in SSD patients to prevent delirium was evaluated in one study but it did not modify ICU LOS (6.2 (4–8) vs 7 (4–9) days, $p = 0.63$ and 2 (2–3) vs 3 (2–3) days, $p = 0.517$) or mortality (9 (25.8%) vs 7 (20.4%), $p = 0.51$).

Conclusion: Subsyndromal Delirium is a common and adverse condition that is manifested in almost one-third of ICU patients. According to our findings, SSD has increased the length of hospital stay only with low impact on the other outcomes. Nevertheless, studies on a bigger sample size and larger scale are needed for a better understanding of the relevance of SSD in ICU patients as well as its treatment.

Keywords: Delirium, Intensive care, Outcome, Critical care, Cognitive abnormalities.

INTRODUCTION

The cause/effect and correlative complexities of illnesses affecting mind and body have moved into the mainstream of critical care medicine over the last decade[1]. Back then, researchers and clinicians have become aware of the importance of delirium in the ICU. In 2004, a landmark study by Ely *et al*. reported ICU delirium as an independent predictor of mortality as well as length of stay and cognitive impairment at hospital discharge[2].

Delirium in the critically ill is common , morbid [3], and distressing . These considerations as well as expert guidelines [4] have fostered initiatives for reliable, easily applicable screening tools. Numerous tools are available to assess delirium in hospitalized patients outside the ICU [5]. Two scales tailored to mechanically ventilated patients have been validated to screen for delirium in the critically ill: the Intensive Care Delirium Screening Checklist (ICDSC) [6],and the Confusion Assessment Method-ICU[7]. Each has been used as dichotomous marker for delirium, i.e., they indicate that the patient either has delirium or does not.

Importantly, various studies report wide ranges of ICU delirium incidences [8].While some of this variation may be related to semantics[9] , other issues such as ICU patient population, presence of unrecognized chronic brain dysfunction, sedation practices, and timing of assessment(s) are other likely contributors to this variance. Furthermore, existing evidence suggests that ICU delirium is not a "one-size-fits-all" phenomenon. It is important to distinguish hypo- from hyperactive delirium, since the former may be associated with a worse outcome [10]. More recently it has become clear that delirium in the ICU appears to

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exist across a spectrum of severities. Furthermore, there is a milder state of syndromal delirium defined as subsyndromal delirium which is characterised by the presence of certain delirium symptoms but without meeting full diagnostic criteria thresholds - is also prognostically important, with intermediate outcomes between full and no delirium [11]. Moreover, it's is some evidence suggesting that the burden of persistent delirium (days of delirium) could be a better measure than merely noting whether it ever occurs [12].

MATERIALS AND METHODS

Eligibility criteria

- All full-text original articles published in peer-reviewed journals
- Only articles published in English were included in the search.
- Only Prospective observational cohorts or clinical trials of adult (>16 years old) patients admitted to the ICU were considered.
- Eligible articles should include a validated screening or diagnostic instrument for delirium (CAM, CAM-ICU, ICDSC, DSM-IV TR, DSM-V)
- Articles meeting the outcomes of the study; reporting one of the outcomes (hospital and ICU LOS, MV duration, death in the ICU, conversion from subsyndromal delirium to delirium, or any post-hospital discharge outcome.

Exclusion criteria

- Review articles, conference and meeting abstracts, letters and editorials were excluded.
- Studies considered by our assessment table to be of poor quality were excluded from the meta-analyses.
- Articles emrolling patients with traumatic brain injury, central nervous system infections, brain tumors, recent intracranial surgery.

Search strategy and search terms

In co-operation with a librarian, we searched the following databases: EMBASE (1974 to September2017), MEDLINE (1946 to September 2017) and the Cochrane Library (up to September 2017). All word variations and thesaurus terms connected to "Delirium" and "Intensive care unit" in the respective search engines were combined with the word variations and thesaurus terms of "SSD" and "critical care". Reference lists of electronically identified publications, including review articles, were screened for studies that were not identified by the initial data search.

Study selection

Authors independently screened the titles and abstracts of all records identified in the searches. Disagreements were resolved via discussion. A data extraction form that included study design, provider type, patient category and outcome data was developed.

Data extraction

Baseline characteristics (study location, period of enrollment, type of ICU, patient enrollment criteria, number of patients enrolled, methods used to identify delirium, duration of follow-up Primary outcome: mortality (ICU and hospital) Secondery Outcomes: Conversion to delirium, mortality in the ICU and hospital, ICU and hospital LOS, and duration of MV

Newcastle–Ottawa Quality Assessment Scale (NOS) was used for evaluation of quality of the studies[13].

Data synthesis and analysis

Risk ratios (RRs) calculation was done to measure the strength of the relationship between SSD and mortality with 95% confidence intervals (CIs). We selected the risk ratio as a measure of effect for the binary outcome (death) since it is less prone to artificial inflation due to heterogeneity than risk difference. For continuous outcomes, we calculated the weighted standard mean difference (SMD) based on reported means or medians.We used the I^2 test to describe the proportion of the total variation in the study estimates that is due to heterogeneity in the meta-analysis. We performed all analyses using Review Manager version 5.3 [14].**The study was done after approval of ethical board of King Abdulaziz university**.

RESULTS

From 1134 citations, we selected 174 studies for further evaluation. After a detailed assessment, we included only 5 studies (2453 patients). We excluded 92 studies for the following reasons: inclusion criteria were not met ($n = 21$); presented as posters, conference abstracts or letters ($n = 40$); irrelevant study endpoint ($n = 9$); only abstracts were available ($n = 6$); duplicate data ($n = 11$); and could not be translated from the language of publication ($n = 1$).

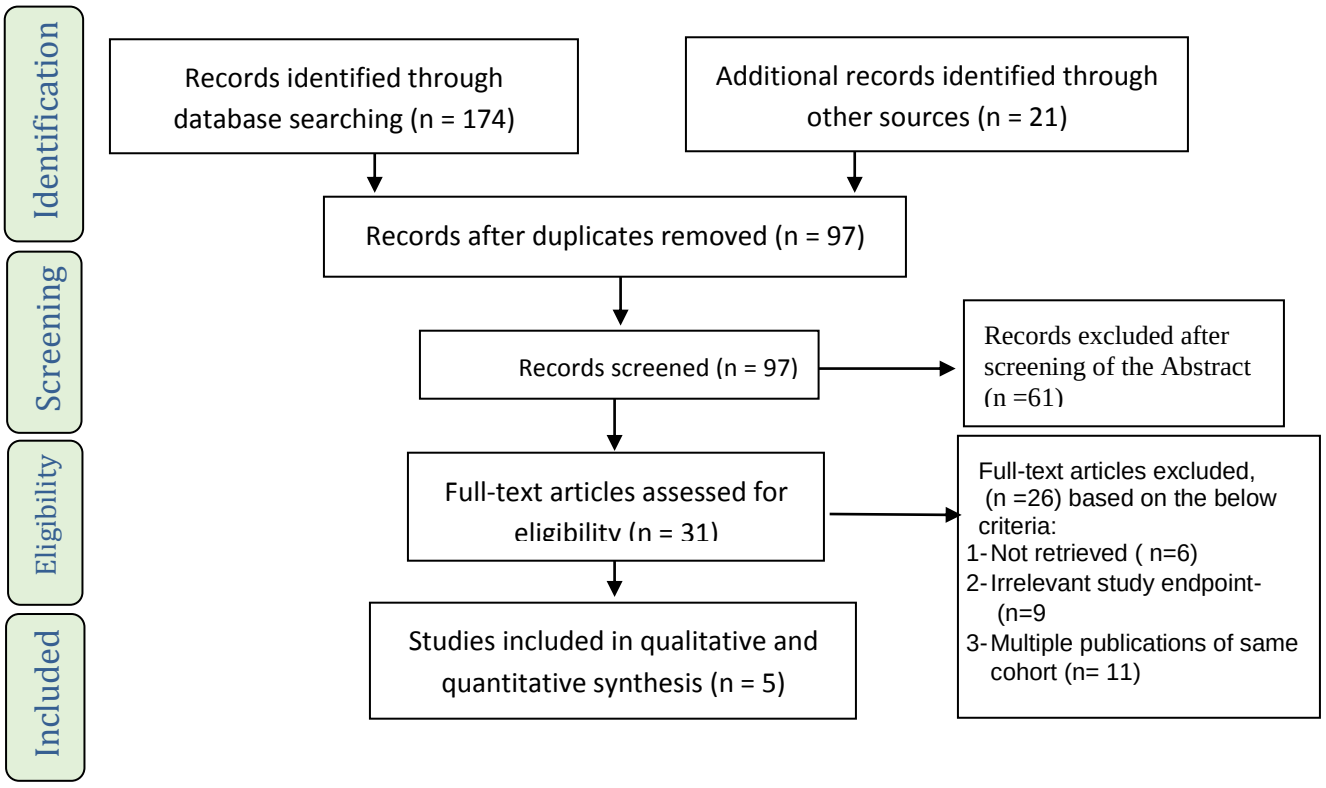

Figure 1: PRISMA flow diagram showing the selection criteria of assessed studies[15]**.**

The search yielded five studies involving 2453 patients. SSD was detected in 849 patients (34.6%). Three studies evaluated only surgical patients. Three studies used the Intensive Care Delirium Screening Checklist (ICDSC) and two used the Confusion Assessment Method (CAM) score to diagnose SSD. Characteristics of the six studies which evaluated sub-syndromal delirium are presented in table 1

Table 1: Baseline characteristics of the included studies.

Authors	Year of publication	Sample Size	Patients' condition	Delirium screening tool	Patients with SSD, *n*(%)		Patients with Delirium	
					(n)	%	(n)	%
Oiumet et al. [16]	2007	537	Medical/surgical	ICDSC	179	33%	189	35%
Tan et al. [17]	2008	53	Cardiac surgical	CAM	18	34%	12	23%
Li et al. [18]	2015	38	Surgical	CAM	13	34%	7 (	8%)
Breu et al. [19]	2015	467	Cardiac surgical	ICDSC	158	39%	54	2%)
Al-Qadheeb et al. [20]	2016	1358	Mechanically ventilated	ICDSC	481	35%	282	37%

CAM Confusion Assessment Method, *ICDSC* Intensive Care Delirium Screening Checklist

The selected studies were well designed and the Newcastle–Ottawa quality assessment demonstrated a low bias risk in most of them

Table 2: Hospital Length of Stay and quality assessment of the included studies

Authors	Non delirium vs delirium patients (factors observed)	Standard deviation of Hospital Length of Stay			Newcastle –Ottawa Scale
		SSD groupdays	Delirium group, days	Non-delirium group, days	
Oiumet et al. *[16]*	1. Age : adverse relationship 2. Had a higher proportion of surgical admission 3. Had the lowest Acute Physiology and Chronic Health Evaluation (APACHE) II scores at admission	40.9 (47)*1	36.4 (28.9)*2	31.6 (46.5)*1,2	7
Tan et al. *[17]*	Not reported	NA	NA	NA	5
Li et al. *[18]*	1. Received fewer blood transfusion unit 2. Presented intraoperative hypotension for a smaller period of time	18.9 (7.5)	22.4 (13.9)+	14.2 (3.7)+	6
Breu et al. *[19]*	1. Aged (non delirium patients were younger 2. Had less duration of extracorporeal circulation (91.4 ± 34.0 vs 109.6 ± 49.6 vs 113.2 ± 44.7 min, p < 0.01)	9.0 (3.8)	11 (6)*	8.0 (2.0)*	5
Al-Qadheeb et al. *[20]*	Not reported	NA	NA	NA	5

Values are shown as means (SD) or *n* (%) as indicated
*$p < 0.01$, $^{+}$ $p = 0.49$
NA not available, Newcastle–Ottawa scale: quality assessment scale, , *SSD*subsyndromal delirium

PRIMARY OUTCOMES

1. Length of hospital stay

SSD prevalence and hospital LOS were the most frequently reported outcomes

since SSD was detected in 849 patients (34.6%). Hospital LOS was described and compared between SSD, delirium, and non-delirium patients in only three studies SD was associated with longer hospital LOS when compared with non-delirium patients after meta-analysis performance (SMD 0.29 (95% CI 0.11–0.48), $p = 0.002$; $I\,2 = 33\%$).

2. Mortality

Ouimet *et al.* **[16] and Breu *et al.*** **[19]** evaluated the association of SSD with mortality.The former reported an increased ICU mortality in the SSD group (10.6% vs 2.4%, p = 0.002) in comparison to patients with no delirium, however in a post-ICU follow-up and after age adjustment, APACHE II score, and

medication-induced coma, the mortality rate was alike(hazard ratio 0.93 (0.58–1.43), p = 0.88) when compared to patients with no delirium. The study of Breu et al. found that hospital mortality rates were comparable between SSD and patients with no delirium patients (4 (1.0-6.9) vs 9 (3.6-20.4), p = 0.05).

3. Impact of SSD treatment

Al-Qadheeb et al. [20] described that the use of intravenous haloperidol 1 mg against placebo in 6 h interval in SSD patients did not prevent conversion to delirium (12 (35.3%) vs 8 (23.5%), p = 0.29) or the time to first delirium occurrence (2 (2–3) vs 3 (2–4) days; p = 0.22), did not reduce delirium duration (2 (1–2) vs 3 (2–4) days, p = 0.261), ICU LOS (6.2 (4–8) vs 7 (4–9) days, p = 0.63), days on MV (4.5 (3–7) vs 5 (3–8), p = 0.79), or ICU mortality (9 (25.8%) vs 7 (20.4%), p = 0.51). In this study the sole observed difference was a reduced duration of agitation (0 (0–2) vs 2 (1–6) h, p = 0.008) in those receiving antipsychotics.

DISCUSSION

This present systematic review and meta-analysis suggested that an entity of "subsyndromal" delirium exists in critically ill patients, and that it is associated with clinically important adverse outcome. Patients presenting with this syndrome fall into an intermediate category which differs from both "no delirium" and "clinical delirium".

The SSD was not consistently associated with increased mortality or worse outcomes, as opposed to current data on delirium[21].Yet, our meta-analysis found an increase in hospital stay. Nevertheless, a solitary study evaluated the association of SSD with duration of MV and was not able to report a clinically relevant outcome[19], although the current literature supports the hypothesis that delirium is independently associated with an increase in MV duration [21].

Recognition of a spectrum of incidence and of effect may also provide a partial explanation for the widely discrepant reported incidences of delirium in ICU. Various authors have reported incidences ranging from 11% [22] to over 80% [1].Screening and diagnostic methods differ among such studies and may include patient assessments performed at different times during the ICU day. Only 30.2% of our cohort never manifested any of the ICDSC items; these patients would likely have been considered cognitively normal by most assessors. This means that 70% of our patients did at some time during their ICU stay demonstrate at least one feature of delirium. Despite not fulfilling psychiatric criteria for clinical delirium, it is possible that application of a sensitive tool would detect an incidence of delirium of up to 70% in a population with characteristics similar to those of the current cohort.

Furthermore, the conversion of mental status or percentage of transition from SSD to delirium was only evaluated in one small-sample clinical trials to describe the effect of antipsychotics in preventing the conversion from SSD to delirium [20]. In the study of **Al-Qadheeb *et al.*** [20]**,** 1358 patients were evaluated but only 68 patients were classified as SSD and received intervention.

CONCLUSION

Subsyndromal Delirium is a common and adverse condition that is manifested in almost one-third of ICU patients. According to our findings, SSD has increased the length of hospital stay only with low impact on the other outcomes. Nevertheless, studies on a larger sample size and scale are needed for a better understanding of the relevance of SSD in ICU patients as well as its treatment.

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