PHENOMENOLOGY AND DIAGNOSTIC CRITERIA FOR DELIRIUM AND SUBSYNDROMAL DELIRIUM IN A POPULATION WITH HIGH PREVALENCE OF DEMENTIA. AN EMPIRICAL STUDY.

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PHENOMENOLOGY AND DIAGNOSTIC CRITERIA FOR DELIRIUM AND SUBSYNDROMAL DELIRIUM IN A POPULATION WITH HIGH PREVALENCE OF DEMENTIA. *AN EMPIRICAL STUDY*.

Doctoral Thesis

Directed by
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Department of Medicine and Surgery

UNIVERSITAT ROVIRA i VIRGILI

Reus
2016

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I STATE that the present study, entitled “PHENOMENOLOGY AND DIAGNOSTIC CRITERIA FOR DELIRIUM AND SUBSYNDROMAL DELIRIUM IN A POPULATION WITH HIGH PREVALENCE OF DEMENTIA. *AN EMPIRICAL STUDY*” presented by Esteban Sepúlveda Ramos for the award of the degree of Doctor, has been carried out under my supervision at the Department of Medicine and Surgery of this university and fulfils the requirements to obtain the European Mention.

Reus, July 6, 2016

The Doctoral Thesis Supervisors,

Joan de Pablo Rabassó

José Gabriel Franco Vásquez

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A Ramon,
perquè amb tu tot té sentit.

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ACKNOWLEDGMENTS

First of all, I wish to thank the directors of my thesis, José Franco and Joan de Pablo, for their guidance and support in the different stages of this long process.

Many thanks also to all the co-authors of the articles, with whom I have worked and discussed throughout this research. A special mention is due to Paula Trzepacz for all her help and comments.

A big 'thank you' to the *"Centre Sociosanitari Monterols*" director, Imma Grau, the team and patients -they have been the essence of this project. To the *Institut Pere Mata* research area director, Elisabet Vilella, and to the team for their help and support. A special thanks to Tania Olivares for her help and patience in the final edition of this work.

I am indebted to the Cognitive Impairment Research Group (CIRG) of the University of Limerick, especially to its director, David Meagher, and the Sligo Mental Health Services in Ireland for taking me as part of their team.

A special mention is due to Maeve Leonard (*in memoriam*), whose warmth, friendship and professionalism accompanied me at every moment during my stay in Limerick.

To Jose and Ana, for sharing this journey with me, and all the things I have learnt from them.

To Ramon Boixadera, for his help and advice, and for his comprehensive and critical review of this thesis.

To my parents and brothers, for being always by my side. To all my family and friends -thanks to them, I never gave up.

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ABBREVIATIONS

AUC: Area Under the Curve.
APA: American Psychiatric Association.

CA: Cluster Analysis.

CAM: Confusion Assessment Method.

CCI-SF: Charlson Comorbidity Index, Short Form.

CDT: Clock Drawing Test.

CI: Confidence Interval CT: Computed Tomography.

CTD: Cognitive Test for Delirium.

DI: Delirium Index.

DSI: Delirium Symptom Interview.

DSM: Diagnostic and Statistical Manual of Mental Disorders.

DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, 3rd edition Revised.

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition.

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition.

DRS: Delirium Rating Scale.

DRS-R98: Delirium Rating Scale – Revised 98.

EEG: Electroencephalogram.

FSD: Full Syndromal Delirium

GH: General Hospital

ICD-10: International Classification of Diseases, 10th edition.

ICDC: Intensive Care Delirium Screening Checklist.

ICU: Intensive Care Unit.

K: Kappa Index.

MDAS: Memorial Delirium Assessment Scale.

MMSE: Mini Mental State Examination.

MRI: Magnetic Resonance Imaging; fMRI: functional MRI.

NH: Nursing Home.

NDND: No-Delirium/ No Dementia

ROC curve: Receiver Operating Characteristics curve.

S-IQCODE: Spanish-Informant Questionnaire on Cognitive Decline in the Elderly.

SD: Standard Deviation.

SE: Standard Error.

SPECT: Single Photon Emission Computed Tomography.

SSD: SubSyndromal Delirium.

STARD: Standards for Reporting of Diagnostic Accuracy guidelines.

TMT-B: Trail Making Test B.

WHO: World Health Organization.

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SUMMARY

Although delirium is a syndrome that has been known since Hippocratic times, the term itself became consolidated only after the publication of the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III) in 1980.

Changes in successive editions of the DSM have focused on improving the reliability of this diagnosis, but it has been reported that these changes could have compromised its validity. On the other hand, ICD-10 criteria have been shown to be very restrictive and to have poorer reliability and validity values than their DSM counterparts. Overall, the different criteria did not cover the same groups of subjects.

New DSM-5 criteria were created in continuity with prior editions, but validity and reliability studies are still scarce.

Subsyndromal delirium (SSD) has been defined in the DSM-5 as an attenuated syndrome, but without specific criteria for diagnosis. Studies using categorical or dimensional approaches show that different methods cover different types of subjects, but SSD outcomes and risk factors are consistently similar with those of Full Syndromal Delirium (FSD).

A recent new proposal, which has not been fully studied yet, defines SSD as an acute or subacute onset of symptoms (altered attention and evidence of other cognitive and/or neuropsychiatric disturbances) in the absence of FSD.

In addition to the different clinical criteria for delirium diagnosis, we have different kind of scales for evaluation. The DRS-R98 evaluates a wide range of delirium symptoms, covering their breadth in anchored descriptions, which are not based in any *a priori* classification system. The scale has been translated and validated in several languages in different settings, exhibiting good accuracy against the DSM-IV diagnosis of delirium and good inter-rater reliability values. However, the best cut-off score, sensitivity and specificity values for the Spanish version of the scale have not yet been established.

Dementia is both a risk factor and a possible adverse consequence of delirium and when delirium and dementia coexist, there are poorer outcomes than when they do not concur. Although delirium symptoms overshadow those from dementia, the coincidence of some symptoms, especially those about cognition, entails a challenge for diagnosis. Therefore, accurate and reliable instruments for delirium evaluation are particularly important in demented populations, for whom more studies are needed.

Progress in the nosology of delirium requires a better understanding of its phenomenology and the extent to which clinical criteria actually cover the syndrome. Our aim in this work was to evaluate the performance of DRS-R98 in

our population against different diagnostic criteria and later to analyse how well they represent the delirium entity, including the under-studied SSD.

This work is composed of three studies. The aim of the first study was to evaluate the performance of the DRS-R98 against five delirium diagnostic classifications (DSM-III-R, DSM-IV, DSM-5 and ICD-10) in a population with high prevalence of dementia and to test the diagnostic concordance of these five categorisations. This was a cross-sectional prospective study of 125 patients admitted to a skilled nursing home, whose delirium status was determined by one researcher using each of the five diagnostic classifications and, independently, by another researcher using the DRS-R98. The dementia status was determined using the Spanish- Informant Questionnaire on Cognitive Decline in the Elderly (S-IQCODE). Diagnostic classifications only coincided in 52.8% of cases, where the DSM-IIIR diagnosed most cases (27.6%) and the ICD-10 the least (16%). The accuracy of the Spanish DRS-98 (evaluated through Receiver Operating Characteristics (ROC) curves) was higher than 90% against the delirium diagnosis by any classification, performing best against DSM-IIIR and worst against ICD-10. The performance of the scale was worse in subjects with dementia under any diagnostic classification, but was still good (> 86%). The best cut-off score of the scale was >14.5 under any DSM edition and >15.5 under ICD-10.

For the second study, the aim was to test the accuracy of the five diagnostic criteria against an “agnostic” reference, created through the natural grouping of symptoms by cluster analysis of DRS-R98 items and to determine the inter-rater reliability of the diagnostic criteria. In this study the sample was widened to 200 subjects, in the same facility and conditions, evaluated by one researcher through the DRS-R98 and with the clinical diagnostic criteria being administered independently by two professionals from different disciplines (a psychiatrist and a psychologist) to determine inter-rater reliability through the Kappa index. The accuracy of all diagnostic criteria was good. DSM-IIIR obtained the best result (87.5%), the best sensitivity (81.6%) and most balanced sensitivity/specificity values, but the worst inter-rater reliability (0.62). The best inter-rater reliability was displayed by the DSM-5 (0.73). All values dropped in the sub-sample of patients with dementia.

Finally the aim of the third study was to evaluate the phenomenology of subjects diagnosed with SSD under the aforementioned new proposal in comparison with subjects suffering from FSD (DSM-5), dementia or neither, drawn from two different geriatric settings. In this study we used data from 200 subjects of the same skilled nursing home and 200 patients from a general hospital, evaluated independently by two researchers, one of the basis of DSM-5 and the other on the basis of DRS-R98. The four sets were significantly different in total DRS-R98 scores, in severity DRS-R98 scores and in symptoms from the three core domains (circadian, cognitive and higher level thinking). The scores increased stepwise as follows: No Delirium No Dementia < dementia-only < SSD < FSD. FSD and SSD were phenomenologically similar in both clinical settings. In subjects with dementia, the results were similar.

The low concordance of diagnostic criteria, also in the newest DSM edition (DSM-5) shows that they cover only partially and in a different extent the complexity of

the delirium syndrome. Some subjects that failed to classify for DSM-5 showed symptoms of intermediate intensity between FSD and non-delirium consistent with an SSD diagnosis.

The DRS-R98 performed very well in our population with high prevalence of dementia. The groups delineated through the DRS-R98 were useful as a pattern to compare diagnostic criteria, confirming that DSM-IIIR criteria have the best sensitivity/specificity balance, probably because of a better inclusion of core delirium symptoms. The core delirium symptoms were found to be useful in the differentiation of FSD and SSD from no-delirium dementia and no-delirium no-dementia subjects. All these findings support the necessity of including these symptoms in diagnostic criteria, with clearer and anchored questions that improve their reliability and with the support of a biomarker to enhance their accuracy.

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1. INTRODUCTION

1.1. Historical context

Delirium symptoms have been described as part of entities with different names since Ancient literature. *Phrenitis* was one of the core categories of Greek psychiatry (along with *mania*, *melancholia* and *paranoia*)[1] and denoted a mental derangement, associated sometimes with speech, motor and sleep disturbances, related with humours alterations or other diseases [1,2]. The word came from "*phrēn*" which meant the part of the body thought to be responsible for reasoning and intelligence since Homeric times [2].

Hippocrates used several words to refer to *phrenitis, (leros, paraphrosyne, paraleros, lethargus, etc.)* corresponding to what we now know as delirium [3]. From the Hippocratic Corpus onwards, for most ancient authors (such as Diodes of Carystus, Praxagoras of Cos, Aretaeus of Cappadocia and Galen) *phrenitis* was associated with high mortality rates and fever was a cardinal and necessary symptom. The main affected place in the body changed from the diaphragm to the heart or the brain for Galen, or even to no identifiable location for Caelius Aurelianus. Illusions, hallucinations and fluctuating course were symptoms frequently described and treatment was based on removing the causative agent [2].

Celsus, in the first century AD, was the first one to use the term "*Delirium*" instead of *phrenitis* to refer to a mental syndrome developed as a consequence of fever or head trauma. The name comes from the Latin *deliro-delirare* (de-lira**,** to go out of the furrow). He was possibly the first one to relate this syndrome to conditions occurring without fever [3].

In Constantinople (VI century AD), the historian Procopius described symptoms in patients probably suffering from bubonic disease and experiencing motor agitation and insomnia or lethargy and motor retardation, similar to what we now know as hyperactive and hypoactive delirium, respectively [3].

During the sixteenth century, the surgeon Ambroise Pare, described delirium symptoms as a post-surgical complication. For Philip Barrought, writing in 1593, *phrenesis* was an incurable and deadly disease, though a few patients would survive while still suffering from a loss of memory and reasoning [3]. For Thomas Williams (1621 - 1675), in his theory of animal spirits, when "*foolishness"* (a group of diseases altering thinking and sensorial perception) coexisted with fever it would become a delirium (of brief duration) or a "*phrenzie"* (a more prolonged condition). He also thought that other causes aside from fever could cause delirium, such as alcohol, hysteria or poisons and that its prognosis depended of the nature of the underlying causes, the patient's age and previous health [4].

There are also some reports of delirium symptoms from other cultures. It has been suggested than in the Judaist Talmud, the Greek word *Kordiakos* meant a reversible madness after drinking alcohol, probably related to *delirium tremens* [1]. Najab ub din Unhammad, an Arab physician of the eighth-century called "*Souda a Tabee"* a febrile delirium and for the Persian Razhes "*Sirsen*" described both hypoactive and hyperactive delirium due to fever or excessive drinking [3].

At the beginning of the nineteenth century, Sutton suggested that affective and motor disturbances were also part of the syndrome [1] and introduced Delirium *tremens* (from the tremor of the hands), as a diagnosis associated to alcohol intake [3]. At that moment, the term Delirium had a double meaning in most European countries, being especially problematic in France where "*délire*" meant both what we know as "delusions" and *phrenitis* (cf. Pinel, Esquirol, Georget...). However, by 1860 "délire" became mostly associated with the abnormal ideas during delirium while the term "confusion" was used in the modern sense of "syndromic" delirium by authors such as Delasiauve.

For Chaslin, in his *Confusion Mentale Primitive* (1895), the main alteration in "confusion" was a loosening of synthesis capabilities affecting intellectual, affective and volitional functions. The concept was linked to an alteration in consciousness, which was deteriorated but less so than in "stupor". For him, the syndrome was due to cerebral weakness and was equivalent to the "crepuscular state" of German psychiatrists. It was characterized by difficulties in attention, orientation, memory, visuospatial and intellectual capacities, as well as slow and difficult movements, and patients could also suffer delusions, hallucinations, illusions, emotional reactions, intellectual excitation and agitation. This state could last from days to months and prodromal symptoms could appear, along with affective alterations, insomnia, nightmares, pain or weakness [3,5]. As we can see, his semiologic description of the syndrome is very close to our own.

During the middle of the nineteenth century, some authors (such as Brierre de Boismont and Calmeil) considered delirium to be part of a continuum with "insanity", on the basis of the popular doctrine of unitary psychoses [1]. Many authors followed Greiner [3] in positing consciousness alteration as the characteristic symptom of delirium differentiating it from other psychoses, though others differed (cf. Kraepelin, Manfred Bleuler and Klaus Conrad).

When Bonhoeffer published his work on "symptomatic psychoses" at the beginning of the 20th century, he used the expression "*Die exógene reactions Typus*", to define a reaction of the brain to physical illness characterized by clouding of consciousness [3,6,7]. Kurt Schneider (1947, 1948) stated that clouding of consciousness was an essential feature of what he termed "physically related psychoses"[3].

Engel and Romano in the 1940s [8–10] stated that delirium is due to a cerebral insufficiency (with a reduction of the metabolic rate), provoking a non-focal slowing of the EEG. They also claimed that such changes were potentially reversible if the underlying condition improved and were correlated with the level

of consciousness and cognitive abilities. This is probably the first attempt to link clinical features with a possible biomarker in delirium.

Since the mid-twentieth century the evolution of delirium conceptualisation has revolved around the classifications of the American Psychiatric Association (APA) and the World Health Organization (WHO) forming the basis of current clinical study. They will be described next.

1.2. The Clinical Criteria for Delirium evolution

In 1952 the APA, published the first edition of the Diagnostic and Statistical Manual of Mental Disorders [11] in order to provide an unified classification of psychiatric disorders for statistical purposes. The text was based mainly on a psychoanalytic approach, then dominant in the United States. A second edition, the DSM-II [12], was published to coincide with the eighth edition of the International Classification of Diseases, ICD-8 [13] with only few changes [14]. In both works, delirium did not exist as a category, despite its long history in European psychiatry. Instead, it was part of a broader group of "acute brain syndromes", where the "acuteness" referred to its probable reversibility. As with other disorders associated with the impairment of the brain tissue function, this diagnosis was characterized by the alteration of orientation, memory, intellectual functions (comprehension, calculation, knowledge, learning, etc.), judgment and lability and by the shallowness of affect, though psychotic, neurotic or behavioural manifestations could also be present.

Table 1.1. DSM-III Diagnostic criteria for Delirium

A. Clouding of consciousness (reduced clarity of awareness of the environment), with reduced capacity to shift, focus, and sustain attention to environmental stimuli.
B. At least two of the following:
    1. Perceptual disturbance; misinterpretations, illusions, or hallucinations.
    2. Speech that is at times incoherent.
    3. Disturbance of sleep-wakefulness cycle, with insomnia or daytime drowsiness.
    4. Increased or decreased psychomotor activity.
C. Disorientation and memory impairment (if testable).
D. Clinical features that develop over a short period of time (usually hours to days) and tend to fluctuate over the course of a day.
E. Evidence, from the history, physical examination, or laboratory tests, of a specific organic factor judged to be etiologically related to the disturbance.

American Psychiatric Association, 1980 [15].

A ground-breaking article was published in 1971 [16] which demonstrated that British and American psychiatrists greatly differed in their diagnosis, notwithstanding the very similar diagnostic categories in ICD-8 and DSM-II. Hence, with the publication of a new edition of the ICD [17], the APA charged Robert Spitzer with the task of redraft the DSM manual on the basis of consensus-based categories [14], leading to the release of the DSM-III in 1980 [15].

"Delirium" was categorized for the first time in DSM-III, unifying all the synonymic diagnosis that had been used in the past [18]. Accordingly, it was provided with specific diagnostic criteria: clouding of consciousness with alteration of attention; at least two of these four items: perceptual disturbances, incoherent speech, sleep-wake disturbances and psychomotor alterations; disorientation and memory impairment; symptom development over a short period of time with a trend to fluctuate; and evidence of probable aetiology (see **Table 1.1**)

Table 1.2. DSM-III-R Diagnostic criteria for Delirium

A. Reduced ability to maintain attention to external stimuli (e.g., questions must be repeated because attention wanders) and to appropriately shift attention to new external stimuli (e.g., perseverates answer to a previous question).
B. Disorganized thinking, as indicated by rambling, irrelevant, or incoherent speech.
C. At least two of the following:
    1. Reduced level of consciousness, e.g., difficulty keeping awake during examination
    2. Perceptual disturbances: misinterpretations, illusions, or hallucinations
    3. Disturbance of sleep-wake cycle with insomnia or daytime sleepiness
    4. Increased or decreased psychomotor activity
    5. Disorientation to time, place, or person
    6. Memory impairment, e.g., inability to learn new material, such as thenames of several unrelated objects after five minutes, or to remember past events, such as history of current episode of illness
D. Clinical features develop over a short period of time (usually hours to days) and tend to fluctuate over the course of a day.
E. Either (1) or (2):
    1. Evidence from the history, physical examination, or laboratory tests of a specific organic factor (or factors) judged to be etiologically related to the disturbance
    2. In the absence of such evidence, an etiologic organic factor can be presumed if the disturbance cannot be accounted for by any nonorganic mental disorder, e.g., Manic Episode accounting for agitation and sleep disturbance

American Psychiatric Association, 1987 [19].

The revised version of this third edition in 1987 [19] included some changes (**Table 1.2**), as the exclusion of the vague and operationally difficult "clouding of consciousness", replacing it with the mere alteration of attention, now defined as a reduced ability to maintain or shift attention to external stimuli. The new edition

also introduced a single criterion to evaluate disorganized thinking and reformulated the criterion about aetiology to include the possibility of presumed causation, when other evidence is absent. The DSM-III had the widest range of symptoms for the evaluation of delirium; ever since, as we shall see, they have been successively simplified to ease the understanding and interaction between health professionals

DSM-IV [20] was created in the light of the large quantity of new research based on the DSM-III and DSM-III-R [21], and to coincide with the release of ICD-10 [22,23]. Liptzin [24,25] reported DSM-III-R to be more restrictive than DSM-III criteria, whereas ICD-10 was overly more restrictive than the previous two. Based on those results, and the possibility of difficulties differentiating delirium symptoms from dementia or other underlying conditions, the DSM-IV task force decided a more inclusive "minimal criteria" upon which phenomenological research could be built up [21]. These new criteria (**Table 1.3**) reintroduced disturbance of consciousness in the same item as alteration of attention, added an item for change in cognition or alteration of perception that could not be accounted for by a previous dementia, and maintained the items about acute onset and fluctuation as well as evidence of aetiology. The revised edition did not change these criteria [26].

Table 1.3. DSM-IV Diagnostic criteria for Delirium

A. Disturbance of consciousness (i.e. reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention.
B. A change in cognition or the development of a perceptual disturbance that is not better accounted for by a preexisting, established or evolving dementia.
C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.
D. There is evidence from the history, physical examination or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.

American Psychiatric Association, 1987 [20].

The last edition of this publication, the DSM-5 [27] left delirium diagnostic criteria with only minor modifications. Fundamentally, "awareness" alteration replaced "consciousness" alteration in the first criterion and substituted the term "dementia" for "other neurocognitive disorder" as one of the alternative diagnosis to discard.

The International Classification of Diseases began as the "*Bertillon Classification of Causes of Death"* in 1893 [28,29] but with little mention to mental conditions in its first editions, as far it was conceived as a statistical tool for fatal medical conditions. A chapter on mental diseases was included only in the sixth edition in

1948 when the World Health Organization took over the publication, but it was not until the latest edition in 1992, the ICD-10, when the publication changed its focus from a predominantly statistical to a more clinically descriptive approach [22,23], after consultation with experts from different countries.

Table 1.4. DSM-5 Diagnostic criteria for Delirium

A. Disturbance in attention (ie, reduced ability to direct, focus, sustain, and shift attention) and awareness.
B. Change in cognition (eg, memory deficit, disorientation, language disturbance, perceptual disturbance) that is not better accounted for by a preexisting, established, or evolving dementia.
C. The disturbance develops over a short period (usually hours to days) and tends to fluctuate during the course of the day.
D. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by a direct physiologic consequence of a general medical condition, an intoxicating substance, medication use, or more than one cause.

American Psychiatric Association, 1987 [27].

There are two versions of ICD-10, the "Diagnostic Criteria for Research"[23] and the "Clinical Descriptions and Diagnostic Guidelines"[22]. The latter are intended for "general clinical, educational and service use" and consist more of a general description of the syndrome rather than specific criteria [22]. Research criteria [23] include a broader range of symptoms than those on DSMs because they wanted restrictive criteria in order to get more homogenous groups of patients for research purposes (**Table 1.5**). The first criterion is very similar to DSM-IV', requiring clouding of consciousness and alteration of attention. Another required item is an alteration of immediate and recent memory with disorientation, one psychomotor disturbance (shifts from hypo to hyperactivity, increased reaction time, increased or decreased flow of speech or enhanced startled reaction), one sleep-wake disturbance (insomnia, nocturnal worsening of symptoms or disturbing dreams / nightmares), rapid onset and fluctuation of symptoms and finally evidence for aetiology.

Despite the use of the term "Delirium" in the classifications during the last decades, several others are still used to refer to the same syndrome: "acute confusional state", "acute brain failure", "ICU psychosis", "subacute befuddlement", "acute brain failure" or "organic brain syndrome", among others ([30,31], making health care communication difficult and increasing the possibility of under or misdiagnosis. But, even when the term is the same, changes in "modern" classifications undoubtedly lead to differences in their validity and reliability.

Table 1.5. ICD-10 Diagnostic criteria for Delirium

A. Clouding of consciousness, i.e. reduced clarity of awareness of the environment, with reduced ability to focus, sustain, or shift attention.
B. Disturbance of cognition, manifest by both:
    1. Impairment of immediate recall and recent memory, with relatively intact remote memory;
    2. Disorientation in time, place or person.
C. At least one of the following psychomotor disturbances:
    1. Rapid, unpredictable shifts from hypo-activity to hyper-activity;
    2. Increased reaction time;
    3. Increased or decreased flow of speech;
    4. Enhanced startle reaction.
D. Disturbance of sleep or the sleep-wake cycle, manifest by at least one of the following:
    1. Insomnia, which in severe cases may involve total sleep loss, with or without daytime drowsiness, or reversal of the sleep-wake cycle;
    2. Nocturnal worsening of symptoms;
    3. Disturbing dreams and nightmares which may continue as hallucinations or illusions after awakening.
E. Rapid onset and fluctuations of the symptoms over the course of the day.
F. Objective evidence from history, physical and neurological examination or laboratory tests of an underlying cerebral or systemic disease (other than psychoactive substance-related) that can be presumed to be responsible for the clinical manifestations in A-D.

World Health Organization, 1993 [23].

1.3. Studies on the validity and reliability of criteria

Valid and reliable diagnostic criteria are fundamental to classify delirium correctly and therefore to identify it accurately, decide on an adequate management and determine a real prognosis [32]. Validity of a test or set of criteria involves their accuracy, determined in part through sensitivity and specificity analysis, and usually measured against a "gold standard" that is considered valid.

Without a completely accepted biological marker for delirium, its diagnostic criteria have been the only gold standard for clinical diagnosis until now. However, the use of criteria largely relying on experts' consensus and epidemiological research can be circular [25,33,34]. Further, iterations of diagnostic classification systems may result in different delirium diagnosis status in the same population. Field trials of DSM criteria since DSM-III have passed through different stages, but all of them have been focused on reliability improvement, finishing with the DSM-5, where the intraclass kappa statistics approach was used to measure the agreement between two observers, since the ability of two clinicians to

communicate between them about a specific patient is a good indicator of quality [32].

The introduction of specific criteria in DSM-III in allowed the development of studies about their validity and reliability. Maybe the first of them was the study of Liptzin in 1991 [24,25] in which he found DSM-III-R criteria to be more restrictive than DSM-III but less than ICD-10 (25 patients with DSM-III delirium didn't meet the DSM-III-R criteria and 104 patients with delirium diagnosed both by DSM-III and DSM-III-R were not diagnosed with ICD-10), where differences between the two versions of the DSM-III were accounted mainly by the difficulty to score the item of disorganized thinking in DSM-III-R patients with no verbal communication and to obtain all the required symptoms for the DSM-III-R in the same 24-hour period .

It has been proven in later studies that the simpler criteria in DSM-IV enhance its inclusiveness whereas ICD -10 has been confirmed to be over-restrictive. Laurila et al [33] compared the diagnosis of delirium made by DSM-III, DSM-III-R, DSM-IV and ICD-10 in a group of geriatric patients from acute wards and nursing homes and found that only 5.9% of them met all four criteria, 24.9% met DSM-IV, 19.5% DSM-III-R, 18.8% DSM-III and 10.1% ICD-10 criteria. Interestingly when they made a differential analysis between general hospital wards and nursing homes, DSM-III-R was more inclusive in the second ones than DSM-IV, suggesting criteria performed differently depending on the place and type of patients. In a later study, they analysed the influence of comorbid dementia in delirium diagnosis and found criteria exhibited a similar inclusiveness trend, independently of the presence or absence of dementia [35], but with a significantly larger proportion of patients without underlying dementia diagnosed with delirium by the DMS-IV (23.5% against 13.5% with DSM-III-R, 12.9% with DSM-III and 2.9% with ICD-10).

Cole et al. [36] studied those same criteria (DSM-III, DSM-III-R, DSM-IV and ICD-10) using latent classes analysis (a latent variable model to delineate latent discrete variables from observed discrete criteria that allow describing accuracy among them), in a sample of patients older than 65 from a general hospital ward. They also found that DSM-IV was the most inclusive with sensitivity of 100% but with the worst specificity (84.5%) and, on the contrary, ICD-10 was the most restrictive and obtained the worst sensitivity (63.3%) with good specificity of 95.9%. DSM-III and DSM-III-R had very good sensitivity and specificity values (97.5% and 96.5 for the former and 93.8% and 95.6 for the latter).

In the Laurila et al. works [33,35] criteria were not evaluated directly, but researchers used a set of operationalized symptom. In the Cole et al. study [36], the way diagnostic criteria were operationalized or administered was not specified, which could interfere in their practical interpretation.

Subsequent studies have found similar results, e.g. in patients after cardiac surgery with a delirium incidence of 16.3% with the DSM-IV and 14.2% with the ICD-10 [37], and in long-term care demented residents [38], with values of prevalence of 26.5% for DSM-III, 29% for DSM-IV-TR, 41.3% for DSM-III-R, 45.8% for the Confusion Assessment Method (CAM) algorithm for definite delirium and 70.3%

for the CAM algorithm for probable delirium, with a coincidence of all these classifications in only the 23.9% of cases, which suggests a relatively stable trend throughout different clinical settings.

After publication of the DSM-5, Meagher et al. [39], compared the diagnose made using DSM-IV with DSM-5, obtaining the latter after allocating the evaluated symptoms with the Delirium Rating Scale- Revised 98 (DRS-R98). They evaluated DSM-5 in two possible ways. A "strict" interpretation where for the first criterion both attention and awareness alteration have to be present and for the second criterion both acute onset and fluctuation have to be present. Also, they provided a "relaxed" interpretation with only attention alteration required for the first criterion and either acute onset or fluctuation for the second criterion. All these criteria were tested using the equivalent item in the DRS-R98 (awareness being evaluated through the item of orientation). They found the "strict" DSM-5 to coincide with the DSM-IV in only 53% of cases, with sensitivity of 30% and specificity of 99%, but the "relaxed" interpretation obtained a concordance of 91% (improving sensitivity to 89% and with specificity of 96%).

Recently, Adamis et al. [40] in a study with patients 70 years and older from a general medicine ward, found DSM-5 to be less inclusive than DSM-IV, with a delirium rate of 13% and 19.5%, respectively. This difference was explained mainly by the interpretation of the terms "awareness" and "consciousness", whose alteration was not always simultaneously present in the same subject.

Regarding inter-rater reliability (the measure of the agreement between two independent evaluators). Cameron et al. [41] reported good values for DSM-III criteria, with a kappa coefficient of 0.62. Later, Laurila et al. [33] reported a kappa of 0.72 for DSM-IV, 0.74 for both DSM-III and DSM-III-R and 0.62 for ICD-10. They also obtained the kappa for the individual symptoms or group of symptoms evaluated under the different criteria and found a kappa of 1 for all of them except for clouding / disturbance of conscience (0.72), emotional disturbance (0.62), rapid onset and fluctuation of symptoms (0.72) and causative agent (0.70). The grouping of symptoms may have been unsatisfactory, since their evaluation did not coincide exactly with the way the criteria are stated, leading to a possible divergence with their real use in clinical practice.

Silver et al. [42] found a kappa of 0.94 for DSM-IV delirium in paediatric patients from an intensive care unit, however it should be noted that this high value came from a study with a small number of patients in which researchers had been trained beforehand to get confluent concepts, which is, unfortunately again, distant from daily practice.

Malt et al. [43] confirmed a poor agreement for delirium diagnosis (49.3%) between evaluators from different countries in Europe using the ICD-10 criteria, the worst among 13 psychiatric diagnoses evaluated in the study.

The reliability of delirium diagnosis in DSM-5, unlike that of many other psychiatric disorders, remains still to be established [32].

According to Kendler [44], an "epistemic" iteration, in analogy with mathematics, should allow us to achieve a better approximation to psychiatric diagnoses through a successive improvement on its predecessors, which implies that changes have to be made based on convincing evidence on empirically-defined entities.

In the search for a delirium entity based on empirically-defined symptoms, phenomenological studies have shown some symptoms are more frequent than others, independently of the etiologic cause, which has lead them to be defined as core symptoms in contraposition to the non-core or associated symptoms, that can effectively be associated to specific causes, individual differences in brain circuitry and vulnerability, or greater episode severity [31].

Most phenomenological studies of delirium symptoms, based mainly in the Delirium Rating Scale- Revised 98 (DRS-R98) [45] and the Memorial Delirium Assessment Scale (MDAS)[46], have yielded three core symptom domains: attention and other cognitive deficits, higher level thinking alterations (language, thought process and executive function) and circadian disturbances (including sleep-wake cycle and motor alterations), whereas other symptoms such as delusions, perceptual disturbances or emotional alterations have been classified as associated symptoms [47–57]. In these studies, the most consistently present feature in delirium is attention alteration, which has been cardinal in all delirium diagnostic criteria until now. However, not all core symptoms are consistently taken into account and current criteria (ICD-10 and DSM-5) give excessive weight to non-core symptoms.

To continue evolving in diagnostic delirium systems, they should be compared to a "gold standard", in order to improve their validity and reliability. However, we do not have any "pattern" for comparison, such as a specific biomarker. An alternative method could be to use an "agnostic" approach to categorize delirium based on its features by means of cluster analysis, a multivariate statistical method that identifies groups of cases according to similarity on certain well-accepted characteristics (phenotype) of a specific disorder [58] without the constraint of an *a priori* diagnostic system. Cluster analysis for nosology studies should be performed in populations with a wide range of diagnostic severity and complexity -keeping in mind that the complexity of delirium detection increases when it occurs in the context of other neuropsychiatric disorders, especially dementia [59,60].

1.4. Scales in delirium

Patient's evaluation could be improved with the use of structured scales, since they can facilitate the communication between clinicians and researchers, enhance the probability of diagnosing a specific pathology, especially among non-expert professionals, help to get a more precise diagnosis or to rate the severity of the syndrome or specific features of it, among other advantages. In nosological and phenomenological studies they are useful to have a more stable measure independently of changes in clinical criteria or to test aspects of a symptom or a

range them such as their severity. Here, I will review some of the scales used in delirium, gathered according to their main purpose.

1.4.1 Screening

The most-used screening scale in delirium is the CAM [61], it was developed based on the operationalization of nine symptoms of the DSM-IIIR criteria (acute onset, inattention, disorganized thinking, altered level of consciousness, disorientation, memory impairment, perceptual disturbances, psychomotor agitation or retardation, and sleep/wake disturbance).
In a widely-used shorter version of the scale, in the form of a diagnostic algorithm of four of these symptoms, it is necessary for the possible diagnosis of delirium to determine the presence of acute onset with fluctuating course and of inattention, plus one of either disorganized thinking or altered level of consciousness. In the original validation study, values ranged from 94% to 100% for sensitivity and from 90% to 95% for specificity against the clinical diagnosis made by a psychiatrist, with very good inter-rater reliability (k= 0.81 – 1). There is a Spanish validation of the scale, which obtained also good specificity, sensitivity and inter-rater reliability values [62].

There are variations of this instrument adapted to specific clinical settings, such as the CAM-ICU for the intensive care unit (ICU)[63,64], the emergency room [65,66] and nursing homes [67] adaptations.

The CAM scale has been proposed as the most useful bedside instrument because of its accuracy and quick administration (5 minutes) [68]. However, in reviewing the sensitivity values of the CAM scale, several short-comings have been identified: meta-analysis have highlighted the great variance of these results [69,70], sensitivity is influenced by the previous training of the evaluator [71,72] and its accuracy is compromised by the diagnostic system upon which is compared, having a worse performance against the ICD-10 than against any DSM, or when administered in populations with a high prevalence of other neurocognitive disorders such as depression, dementia or psychosis [73,74]. For these reasons it is strongly recommended that the diagnosis does not only rely on the results of the scale, but also on previous training in its use and on a formal cognitive assessment.

The Intensive Care Delirium Screening Checklist (ICDSC) was specifically created for use in the ICU [75]. It is based on the DSM-IV criteria and it is composed of eight items, with a score from 0 to 8. A score of 4 or higher showed a sensitivity of 99% and specificity of 64% for a diagnostic of delirium in the validation study [75] and 75% and 74% respectively against the ICD-10 diagnosis in a later study [76], with a better sensitivity of 90% and specificity of 61.54% when the cut-off score was changed from 4 to 3. ICDSC pooled sensitivity and specificity values of 74% and 81.9% in a more recent meta-analysis [77], compared with values of 80% and 95.9% for the CAM-ICU.

Additional screening procedures have been defined to overcome the shortcomings of these scales. One example is the suggested single question for screening (Single Question in Delirium, SQiD) which could be suitable for minimally-trained health personnel [78]. This would be: "Do you feel that [patient's name] has been more confused lately?" asked to a patient's relative or friend. Another recent tool, the 4AT 4AT [79,80], evaluates alertness, cognition (through a short cognitive test: the Abbreviated Mental Test-4 [81], AMT-4), attention (evaluated through the Months of the Year Backward") and acute change or fluctuating course. Both have shown good sensitivity and specificity values, which make them worthy of further research.

Other scales of frequent use are the NEECHAM [82], the Delirium Observation Scale (DOS)[83] and the Nursing Delirium Screening Scale (Nu-DESC)[84], designed for the evaluation and follow-up of delirium by nurses.

1.4.2. Cognition scales

Cognition is always affected in delirium, but it is only one of the core symptoms of the syndrome and its affectation is shared by other neuropsychiatric disorders. The Minimental State Examination (MMSE) [85] is probably the most widely used cognitive test. It has been shown to be useful in determining the possible development of delirium when it falls in 2 points (with sensitivity of 93% and specificity of 90%), its possible resolution when it has a rise of 3 points (sensitivity and specificity of 77% and 75%)[86], and to determine an increase in the risk of incident delirium by 5% for each score point lost [87]. Fayers et al. [88] found that items 1 (current year), 4 (date), 12 (backward spelling) and 20 (copy a design) correctly identified the 92% of delirium patients in a geriatric ward, although other neuropsychiatric disorders were not taken adequately into account. A MMSE cut-off score of 24.5 showed to be a good predictor of incident delirium in geriatric hospitalized patients, classifying correctly 79.4% of subjects, and a previous severity of cognitive impairment measured by the MMSE correlated with the severity of delirium in the DRS-R98 [89]. Also, the MMSE items of disorientation in time and space were individual risk factors (predictors) for incident delirium (OR of 4.4 and 3.8) and correctly classified 88.3% of patients during hospitalization [90].

The Clock Drawing Test (CDT) has been shown to be useful in detecting cognitive impairment in a general hospital population [91] and a geriatric ward [92,93], but not to differentiate between different cognitive disorders and was not correlated with the specific diagnosis of delirium by CAM or its severity by the DRS or DRS-98 [92]. However, it was sensitive to an improvement in delirium in a small sample of patients of a general hospital, along with the DRS and the MMSE [94].

The Trail Making Test B (TMT-B) has been reported to be useful in differentiating delirium from non-delirium patients (analysed along with altered EEG and reduced serum albumin)[95], and as a risk factor for delirium when altered [96,97]. Among the tests to evaluate attention, the Months of the Year Backwards has shown to be

a very good option for screening of delirium, with especially high sensitivity values [98,99].

The Cognitive Test for Delirium (CTD)[100,101] was created initially for ICU patients and is based in non-verbal responses, which facilitates the evaluation of patients with motoric or verbal disturbances [102–105]. It evaluates five neuropsychological domains: orientation, attention, memory, comprehension and vigilance and can differentiate delirium from other neuropsychiatric conditions such as dementia, schizophrenia or depression [100,101,104]. It has been proven to have higher scores in patients with dementia superimposed on delirium than in patients with delirium but without dementia [50], it is stable during a delirium or subsyndromal delirium episode [103,105] and changes with improvement [106]. It is also capable of measuring the risk for non-reversibility and mortality in delirium patients [107].

1.4.3. Severity rating scales

The MDAS is a 10-item scale [46], mainly based on the DSM-IV criteria, which includes the evaluation of arousal and level of consciousness, cognition (memory, attention, orientation, thinking disturbances) and psychomotor alterations, each of them anchored in graded severity statements. The scale can be administered repeatedly during the same day. It was developed to be used once the delirium diagnosis was made and it does not have items to evaluate some of the symptoms included in the DSM-IV such as acute onset, symptoms fluctuation or possible aetiological cause. It has usually shown very good specificity values (93.75% to 100%) but, sometimes, with lower sensitivity (68% to 100%) in different settings and, in some of them, with different cut-off values [37,46,53,108–111]. It also correlates very well with MMSE scores in some studies [46,109,112], but not in others [53,110], probably reflecting the heterogeneity of the cognitive alterations in delirium; however, the correlation with other severity scales such as the Delirium Rating Scale (DRS)[46,109,110] and the DRS-R98 [112]are very good. It has been used in phenomenological studies and factor analysis has shown a two-factor structure, referred to in most of the studies as behavioural and cognitive [53,108,109,112].

The Delirium Index (DI) [113,114] is a severity scale based only on the observation of the patient without further information from other sources such as family, nursing staff or medical chart. It is based in a minimum observation of the five first questions of the MMSE and rates seven of the ten symptoms of the CAM (attention, thought, consciousness, orientation, memory, perception, and psychomotor activity; excluding acute onset, fluctuation, and sleep-wake disturbance) from 0 to 3: absent, mild, moderate and severe, with a total score from 0 to 21. In the validation studies it showed good inter-rater reliability and correlation with the DRS [113] and measures adequately the change in symptoms over time [114]. It has also been used to determine and measure the severity of subsyndromal delirium [115–117].

The DRS [118] is a widely used scale, intended to be completed by a clinician with psychiatric training. It contains 10 items that have specific descriptors. The scale has shown excellent internal consistency, reliability and validity values, to differentiate delirium from other cognitive and psychiatric disorders, to be useful in the measure of change and to predict outcomes. However it has also been found to have some weakensses -for example when doing repetitive evaluations, specifically for some items (as those about the temporal onset of symptoms and the underlying medical condition). Also, all cognitive alterations are evaluated in only one item (which could require an additional cognitive test) and psychomotor disturbances are assessed in only one question (without specifying hypoactive and hyperactive symptoms), making it difficult to differentiate among motor subtypes [119].

DRS's limitations were addressed in a revised scale: DRS-R98 [45] that is composed of 16 items divided into two sub-scales, one of 3 items (temporal onset of symptoms, fluctuation and physical underlying condition) for an initial diagnostic rating and another of 13 items to evaluate severity, which can be used repeatedly during the course of the symptoms and emphasize the gradation of symptoms intensity, covering their breadth. The severity scale comprises five different items for cognition (orientation, attention, short and long term memory and visuospatial ability), one for language, another for thought and two for hypoactive and hyperactive symptoms along with -as in the DRS-, for sleep-wake cycle, perceptual disturbances/hallucinations, delusions and lability of affect. All items are scored from 0 to 3, except for two diagnostic items that are scored from 0 to 2, with a maximum score of 46 in total and 39 for the severity scale. It uses phenomenological items, common to the psychiatric language, of known delirium characteristics and it is not based in any (*a priori*) diagnostic system.

The wide range of symptoms covered by the scale, the fact that its approach is not based on any previous classification and the anchored descriptions of symptoms make the scale very useful in many types of works. The DRS-R98 has been used for phenomenological studies of the three core domains of delirium (cognitive, circadian and higher order thinking) and non-core aspects [48,57], cognitive alterations [54,120], motor subtypes [51,121] subsyndromal delirium phenotype [105,122,123] and diagnostic stability of delirium characteristics on time [103,124,125].

The DRS-R98 has been translated into different languages [45,126–133] and in all its validations it has shown very good validity values when compared with a diagnosis made by the DSM-IV, with very good sensitivity and specificity values (sensitivity between 82% and 98% and specificity between 85 and 100%) although at different cut-off scores (possibly as reflect of cultural differences) as well as excellent performance with an Area Under the Curve > 0.9 in ROC analyses. In these studies, it had also proved a very high internal consistency (Cronbach's α between 0.78 and 0.96), inter-rater reliability (intra-class correlation coefficient >0.9), and capacity to adequately differentiate delirium from dementia and other cognitive and psychiatric diagnoses. The DRS-R98 has not been validated against other diagnostic systems different to the DSM-IV, though recently a dichotomic diagnosis made with the DRS-R98 correlated very well with the DSM-5's [40].

The Spanish version of DRS-R98 [126] was validated with inpatients in Internal Medicine, Orthopaedic Surgery and General Surgery wards. The scale showed very good inter-rater reliability (Intraclass Correlation Coefficient of 0.96) and a good correlation with cognitive tests such as the Minimental State Examination (MMSE) or the Orientation Scale. Internal consistency was high for that population (Cronbach's α of 0.78). Validity of the scale was not evaluated, thus we lack a reference for sensitivity, specificity and optimal cut-off scores of the Spanish scale. However, the Colombian adaptation of the Spanish DRS-R98 [129] in internal medicine patients from a university hospital showed good sensitivity and specificity values.

1.5. Epidemiology

Delirium is a very common entity. However epidemiologic studies face the problem of certain specificities of this syndrome such as differences in prevalence and incidence according to the method of diagnosis, the fluctuating course which can bias cross sectional studies, the necessity of association with other underlying medical conditions, the lack of any wholly accepted biomarker, among others [60].

There are some factors linked to a higher risk to develop delirium, such as older age, previous cognitive impairment, greater illness severity and comorbidity, functional dependence, history of previous delirium, visual and hearing impairment, depression, alcohol misuse or neurological injuries. There are also usual precipitating factors such as polipharmacy, use of psychoactive drugs, physical restraints, abnormal laboratory results (renal and electrolytic, i.e.), dehydration, among others [31,134]. In specific studies in nursing homes, delirium has been related with previous cognitive impairment [135,136], depression [135] and physical restraints [136].

Rates of delirium vary widely among settings. People living in the community have displayed the lowest prevalence rates: under 0.5 to 1.3% for elderly people, with the highest rate in those with concomitant dementia [137,138] although in at least another study, subjects with head and neck cancer in outpatient treatment, also an special population, showed a higher incidence of 8.6% [139].

In an acute general hospital, a prevalence rate of 19.3% was found [140]. However, there is an important variability between wards. For example in geriatric medical in-patients, prevalence rates range from 10 to 68.3% and incidence rates from 3% to 29% [140–146], prevalence from 28.6% - 41% in orthopaedic wards [140,147], 7.2% of prevalence in general surgical wards [140] and an incidence of 15.2 to 33.9% for elderly surgical patients [148]. ICU adult patients have shown the highest delirium prevalence rates, between 45% and 87% [149] and ICU paediatric subjects have had prevalence values from 13% to 28%, depending on the diagnosis method [150]. Prevalence values in nursing homes range between 6.5% and 16% [135,136,151,152] and Long Term Care residences of 8.4 – 11.5% [136,153], with higher rates (33.3%) identified in populations with more severe dementia and

physical comorbidity [153]. 26.5% to 70.3% in Long Term Care demented residents depending on the diagnostic system used [38]. In the emergency department, delirium prevails in older patients in a range of 7-10% [154,155].

Most works support higher mortality as an adverse outcome of delirium in different settings: during admission in nursing homes, general and cardiac ICU or acute palliative care [152,156,157] and during the follow-up (six, twelve months and five years, depending of the study) for patients from nursing homes, ICU, general hospital, acute geriatric wards, the emergency department and also for those living in the community [137,138,143,152,155,156,158–164]. Still, some studies have failed to find a relation between delirium and mortality risk [165,166] though this could be partially explained by the small number of patients in their samples.

Delirium has also been associated with other adverse outcomes such as medical or geriatric complications [152], a higher risk to be rehospitalised during the next 30 days and a lower likelihood of discharge to the community [152], a longer stay in the facility [141,152,156,157], institutionalisation [141,144,163,167], functional decline [143,167,168], long-term cognitive impairment, e.g. dementia, after the episode [158,163,167,169,170].

Even though delirium is very common in a variety of settings and has important consequences for patients, their family and the health system, it is frequently under-diagnosed. Non-trained nurses only identified delirium in 19.3% of the cases of CAM-defined delirium diagnosed by trained researchers, which was especially problematic in older people, with visual impairment, dementia or hypoactive delirium [71]. Ward physicians recorded only 40.3% of patients with delirium (diagnosed by the DSM-IV) in an acute geriatric unit compared to 83.1% of the nurses [171]. Another study in an acute general hospital found that 63.6% of nurses identified DSM-IV-diagnosed delirium patients as “confused” and 43.6% had documented the delirium or one of its synonyms in the case notes [140]. Emergency department physicians miss 57% to 83% of delirium cases [155]. This low recognition of delirium has been associated with higher mortality and poorer functional recovery at hospital discharge and after 6 months [172], which underlines the special importance in improving the classification and diagnostic methods and their use by health care professionals.

1.6. Dementia and Delirium

As described before, long-term cognitive impairment has been reported both as a possible risk factor and adverse outcome of delirium [31,134–136,158,163,167,169,170,173] and SSD [115,117,145,174–176]. Moreover, an important clinical situation presents itself when they coexist, as delirium superimposed on dementia. Such co-existence has high prevalence rates: between 22% to 89% [177] and has proven to be very distressing for patients, caregivers and even for healthcare staff [178,179]. Moreover, delirium has shown to be the

most frequent cause of admission to hospitalisation in patients with dementia [180].

It has been reported that the probability of suffering delirium increases with the severity of the previous cognitive impairment [89,90,146,181]. Different types of dementia patients seem to have distinctive risks for delirium. One study reported a higher risk in late-onset Alzheimer dementia than in early-onset Alzheimer or fronto-temporal dementia and also higher risks in vascular dementia than in early-onset Alzheimer disease [181]. Another one [182] found a higher delirium frequency in vascular dementia (34.4%) followed by Lewy bodies' dementia (31.8%) and Alzheimer disease (14.7%, without differentiation between early and late-onset, however), and fronto-temporal (0%), with a risk increment in subjects with comorbid cerebrovascular disease. Finally, a more recent study [180] found a higher frequency of delirium in Alzheimer disease (66.7%) than in vascular dementia (36.5%) or parkinsonism-related dementia (40.7%).

Differences in delirium frequencies in these studies could be explained by the type of admission (scheduled vs. acute) and the underlying possible aetiological causes (determined for instance by the exclusion criteria). Some authors claim that differences between dementia types are probably linked to the more widespread brain damage and cholinergic alterations in those dementias types with the highest delirium risk [182,183].

Delirium superimposed on dementia has been associated in many studies with worse outcomes than delirium without dementia, including more heavily impaired functionality, cognitive deterioration, higher rehospitalisation, institutionalisation or mortality risk [162,167,177,184–187]. Some studies do not corroborate higher mortality risks [160,188], probably reflecting the underlying characteristics and specifics of the factors triggering delirium in these studies. It has also been reported that delirium has a slower resolution when comorbid with dementia [55,184,189,190] and to have higher rates of misdiagnosis, probably influenced by the coincidence of symptoms, leading to rates of non-recognition of delirium states by nursing or medical staff of up to 80%, specially in those patients with hypoactive delirium [71,191–193].

In phenomenological studies, similarities between delirium and dementia have been reported as problematic in the diagnostic process, particularly in reference to cognitive symptoms [35,194]. However, most studies coincide that delirium symptoms overshadow those of dementia and that there is an "additive" phenomenological trend when the co-morbidity exists, specially regarding cognitive symptoms [35,50,55,59,146,184,185,189,195–199]. Some studies have suggested that some symptoms are more frequent in the comorbid group, including psychotic, emotional, motoric and some fluctuation characteristics [189,199,200]. There is some controversy on whether the so-called Behavioural and Psychological Symptoms of Dementia (BPSD) are higher in the co-morbid group [182,201] or not [194].

On the other hand, symptoms of the three core domains (cognitive, circadian and higher level thinking) have demonstrated to be useful to differentiate delirium

with or without comorbid dementia from dementia patients or controls without cognitive impairment [55,59]. These works also emphasize the importance of "attention", which consistently showed to be more impaired in delirium (comorbid or not with dementia) than in dementia without delirium or in controls [59,194,202] across different evaluation systems (DRS-R98 and CTD scales, other tests as the Spatial Span Forward or a special device designed to assess sustained attention). Moreover, the degree of attention impairment is correlated to the alteration in other cognitive symptoms [55].

As mentioned before, attention disturbance is indeed a cardinal symptom in all classifications published until now. Further studies are still needed, however, to evaluate the performance of diagnostic criteria in the very challenging population of people with dementia.

1.7. Subsyndromal Delirium

SSD has been defined by the presence of some delirium symptoms, which do not amount to the "full syndromal" delirium (FSD) diagnosis. This phenomenon has been investigated only recently and none of the classifications released until now has provided specific criteria for it. The DSM-5 [27] refers to SSD only as an "attenuated delirium syndrome", without further detail.

Attempts to delineate SSD have followed two main routes: a "categorical" one, defined by the presence of some delirium symptoms, evaluated through the CAM (commonly 1 or 2 of them), the DI or the DSM that do not amount to a delirium diagnosis (usually by CAM or DSM criteria)[67,115–117,135,139,145,152,174–176,203–205], and a "dimensional" one using particular scores from the DRS-R98 or the ICDSC, which fall below the limit defined for delirium [51,105,151,206–210].

Due to the lack of a clear definition, presentation rates are quite different depending on the criteria used and the setting of the studies. Reported prevalence rates range from 7.2%, in subjects undergoing outpatient treatment for head and neck cancer [139] to 51% in patients from skilled nursing facilities [152], including a variety of facilities including acute surgical and medical hospitalisation, ICU, Step Down Unit and palliative care [38,51,123,135,145,151,174,176,204,205]. Also, incidence rates of 28% in geriatric post-acute units have been reported [174], 33.3% in ICU patients [208], 45.3% in subjects undergoing outpatient treatment for head and neck cancer [139], 34% in post-cardiotomy surgical patients [211] and one study comparing a SSD diagnosis using 1 CAM vs. 2 CAM criteria found values of 5.2% vs. 1.3% per 100 persons/week in long-term care residents [117]. In this context, probably the definition of 2 CAM criteria is closer to a syndromal status, clearly differentiated from other cognitive disorders, as for instance it has shown worse prognosis than subjects without delirium symptoms [117], in contrast with the 1 CAM criterion definition.

Subjects with SSD have shown intermediate outcomes, worse than non-delirium and better or similar to FSD patients in a wide number of variables. These include

the probability to suffer complications during a hospitalisation and to stay longer there, of institutionalisation after discharge, death, cognitive and functional impairment during the follow-up and of rehospitalisation [67,115,117,123,152,174,176,203,204,206,208,210]. SSD also shares development risk factors with FSD, such as older age, previous cognitive impairment, impaired previous functionality, depressive symptoms, residence in an institution prior to hospital admission, severity of the underlying disease, some specific causes of hospitalisation (such as fracture or symptomatic infection), some laboratory results (such as lower haemoglobin and lymphocyte count, and higher creatinine levels) malnutrition, some geriatric syndromes (such as sensorial alterations, altered gait or faecal and urinary incontinence), history of cerebrovascular disease, left ventricular dysfunction, diabetes, a previous delirium episode, the presence of medication-induced coma or use of mechanical ventilation in ICU patients and the use of narcotics prior to a surgery and the duration of surgery , among others [117,145,174–176,208,209,211].

SSD subjects who recovered from the symptoms after an 8-week follow-up showed better outcomes than those who did not, and intermediate outcomes between non-recovering and non-delirium subjects [116] suggesting that efforts to treat symptoms in patients with SSD could improve outcomes. Also, SSD has shown to be a risk factor for the development of FSD [176,209] and it seems that the stronger the SSD symptoms, the higher the FSD risk [176,212]. A pharmacological protocol of analgesia, sedation and use of antipsychotics has been shown to reduce the rate of SSD in the ICU [206] and a pharmacological intervention with risperidone has been shown to reduce the risk of conversion of SSD into FSD [207].

In phenomenological studies, SSD has presented an intermediate frequency of delirium symptoms, as measured by the Delirium Symptom Interview (DSI), and the severity of these symptoms as evaluated by the MDAS or the DRS-R98 lies between those of non-delirium and delirium subjects [51,103,122,145,151,205]. The core delirium symptom of attention has also proved to be cardinal in SSD [123,213].

A SSD group obtained without using any a priori definition, by means of cluster analysis of delirium symptoms measured by the DRS-R98 in 859 international subjects [122], showed that symptoms of the three core domains (circadian, higher level thinking and cognition) correctly classified 79.7% of patients with SSD and were also useful to differentiate them from the non-delirium group, with phenomenological similarity to the FSD group but with lower scores. This team proposed that an acute change from baseline to mild severity on DRS-R98 items for sleep-wake cycle disturbance, thought process abnormalities, orientation, attention and visuospatial ability would define SSD.

Different ways for defining SSD do not cover the same groups of subjects, for example between two categorical definitions (more than 1-CAM symptom without CAM delirium diagnosis vs. more than 2 “core symptoms” without DSM-III-R delirium diagnosis) classified 78 vs. 75 subjects, with coincidence in 68 of them [38]. This fact becomes more evident when a study compared a dimensional definition (DRS-R98 scores between 7 to 11) and a categorical (2- CAM symptoms)

and found a concordance of only 50%, the CAM definition being more inclusive with 41 vs. 24 subjects [123]. In consequence, Meagher et al. in 2014 [123] suggested a new definition of SSD in order to facilitate the comparability among studies, which is based upon four criteria: i) absence of FSD, ii) acute or subacute onset, iii) disturbed attention iv) evidence of other cognitive and/or neuropsychiatric disturbances, measured for instance on the DRS-R98, which are not better accounted for by another neuropsychiatric condition. This definition or its relationship with the specific features proposed by Trzepacz et al [122] has not yet been studied, although the need for research to improve phenomenological distinctions among delirium, SSD and dementias have been emphasised [214].

2. JUSTIFICATION

Multiple changes in the conceptual definition of and the fact that, in last decades, clinical criteria released for the APA and the WHO cover only partially and to a different extent the complexity of the syndrome, call for a deeper study of its nosology and phenomenology.

The investigation of DSM-5 criteria is important in the light of the very few studies devoted to the validity and reliability of its definition of delirium. While some of its characteristics could be inferred from the evolution of past DSM editions, the changes introduced are worthy of specific research on their own.

Also, the syndromic dimension of delirium will not be completely understood without the integration into current criteria of specific features for SSD, which need to be clearly defined.

The DRS-R98 has demonstrated to be a very useful tool for phenomenological and nosological works in delirium. For this reason, it is necessary to validate it in our specific population and to prove its helpfulness as an agnostic reference in this specific context.

Finally, the best population to advance in phenomenological studies is one where comorbidity introduces a diagnostic challenge. Hence, a population with high prevalence of dementia is especially suited to improve our knowledge of delirium.

UNIVERSITAT ROVIRA I VIRGILI
PHENOMENOLOGY AND DIAGNOSTIC CRITERIA FOR DELIRIUM AND SUBSYNDROMAL DELIRIUM IN A POPULATION WITH HIGH PREVALENCE OF DEMENTIA. AN EMPIRICAL STUDY.
Esteban Sepúlveda Ramos

3. GENERAL AIMS AND HYPHOTESIS

3.1. General Aims

- To evaluate the performance of the DRS-R98 scale, Spanish version against different diagnostic criteria for delirium.
- To test the concordance, accuracy and inter-rater reliability of five diagnostic criteria for delirium (DSM-III-R, DSM-IV, DSM-5 and ICD-10).
- To determine de characteristics of the new suggested criteria for SSD [123] in two geriatric populations.

3.2 General Hypothesis

- The DRS-R98 scale, Spanish version, has a very good performance in our population independently of the diagnostic criteria used for diagnosis.
- The diagnostic criteria have low concordance and newer DSM editions obtain higher inter-rater reliability but lower accuracy.
- The proposed definition for SSD has symptoms with intermediate severity between delirium and non-delirium subjects, especially those corresponding with the three core domains.
-

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4. STUDY 1.

Performance of the Delirium Rating Scale Revised–98 Against Different Delirium Diagnostic Criteria in a Population with a High Prevalence of Dementia

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Published in: Psychosomatics 2015; 56:530–541. DOI:10.1016/j.psym.2015.03.005

4.1. Aims

- To evaluate the performance of the DRS-R98 scale, Spanish version, in a population with high dementia prevalence.
- To test the performance of the DRS-R98 against five delirium diagnostic criteria (DSM-III-R, DSM-IV, DSM-5 and ICD-10)
- To determine the concordance among these diagnostic criteria.

4.2. Hypothesis

- The Spanish version of the DRS-R98 shows a very good performance in this special population with a high prevalence of dementia.
- The DRS-R98 is valid and very stable independently of the delirium diagnostic criteria used.
- There is a low concordance among delirium diagnostic criteria, as previously reported, but now including also the DSM-5.

4.3. Methods

4.3.1. Design and Subjects

This is a prospective, cross-sectional study of delirium diagnostic accuracy, designed and reported according to Standards for Reporting of Diagnostic Accuracy guidelines (STARD)[215].

Consecutively admitted patients to a skilled nursing facility (Centro Sociosanitario Monterols, Institut Pere Mata, Tarragona, Spain), were eligible. Patients were admitted from home, general hospital or assisted living/senior community during the 6-month study period. Exclusion criteria were refusal to participate, coma, severe language disorder, or inability to speak Spanish.

This study was approved by our corresponding Institutional Ethics Committee (at Hospital Sant Joan, Reus, Tarragona, Spain). All patients or their proxy, when Mini-mental State Examination (MMSE) score was <24 (routine part of the admission evaluation), gave written informed consent.

4.3.2. Measures

Demographic and clinical data were collected. We also reviewed medical records for a recent diagnosis of delirium.

Charlson Comorbidity Index (Short form; CCI-SF)
Developed from the CCI with similar prognostic value [216], this version is based on history of 8 medical conditions: cerebrovascular accident, diabetes mellitus, chronic obstructive pulmonary disease, congestive heart failure, dementia, peripheral arterial disease, chronic renal failure and cancer. Each of the first six conditions scores 1 point when present, while each of the 7th and 8th score 2 points if present (for a maximum possible of 10). A CCI-SF score of 0 or 1 indicates no comorbidity, 2 low comorbidity, and ≥3 high comorbidity.

Spanish-Informant Questionnaire on Cognitive Decline in the Elderly (S-IQCODE)
This structured interview is composed by 26 questions to an informant about the patient's cognition and function during the preceding five years. Direct scores range from 26 to 130. The validated Spanish version uses cut-off >85 for possible dementia [217].

The Delirium Rating Scale Revised-98 (DRS-R98)
The DRS-R98 [45] includes phenomenological descriptive anchors to rate severity levels for each item (ranging from 0 to 3), with a maximum DRS-R98 Total scale score of 46 and DRS-R98 Severity scale of 39 points. Its 16 items include three diagnostic items (including acute onset and temporal fluctuation) and 13 items which rate the severity of symptoms, including individual items to evaluate core delirium characteristics: attention, short and long-term memory, visuospatial

ability, orientation, sleep-wake cycle disturbances, abnormalities of language and thought process, motor agitation, motor retardation, besides other items evaluating perceptual disturbances, abnormalities in thought content, and affective lability. We used the Spanish version which has very good inter-rater reliability [126].

Clinical Diagnostic Criteria
To define delirium status we used four diagnostic criteria: the Diagnostic and Statistical Manual of Mental Disorders-5, IV and III-Revised editions (DSM-5, DSM-IV and DSM-III-R)[19,20,27], and the International Classification of Diseases 10th edition for research (ICD-10)[23]. We designed a diagnostic criteria checklist to systematically rate each item for all diagnostic criteria dichotomously (as present or not) in order to ensure their complete evaluation.

4.3.3. Procedures

Two trained researchers independently evaluated all subjects 24 to 48 hours after admission to rate the Spanish DRS-R98 and the delirium diagnostic criteria checklist, each covering the preceding 24 hours using all sources of information. A third researcher contacted the family or caregiver to administer the S-IQCODE.

4.3.4. Statistical analysis

Continuous variables are expressed as means ± standard deviation (SD). Chi-square test compared categorical variables (with continuity correction as appropriate) and t test compared continuous variables. Statistical significance was set at $p<0.05$, except for multiple comparisons of DRS-R98 items where p was set at <0.01.

DRS-R98 accuracy, sensitivity, specificity and optimal cut-off scores were obtained with receiver operating characteristic curve (ROC) analysis of the area under the curve (AUC) for the whole sample and for those with dementia, reported with their corresponding standard error (SE). Hanley & McNeil test compared the AUCs for DRS-R98's discriminant performance for diagnostic criteria.

Data were analysed using SPSS 21.0, and Epidat 3.01 (ROC analysis, comparison of AUC, and corresponding graphics). The overlap of the diagnostic criteria is reported with a Venn diagram created on VENNY online program [218].

4.4. Results

4.4.1. Sample Characteristics

Of 141 patients admitted during the study period, 16 were excluded, leaving a sample of 125 participants (see **Figure 4.1** for STARD flow diagram). Mean age

was 78.73±9 years and 50.4% were women. **Table 4.1** shows demographic and clinical characteristics by delirium and nondelirium groups according to DSM-5 criteria for the whole sample and the subsample with dementia. The delirium group was significantly older and had higher dementia prevalence.

Figure 4.1. Flow diagram of participants.
Study of the DRS-R98 performance against different delirium diagnostic criteria in patients with high dementia prevalence.

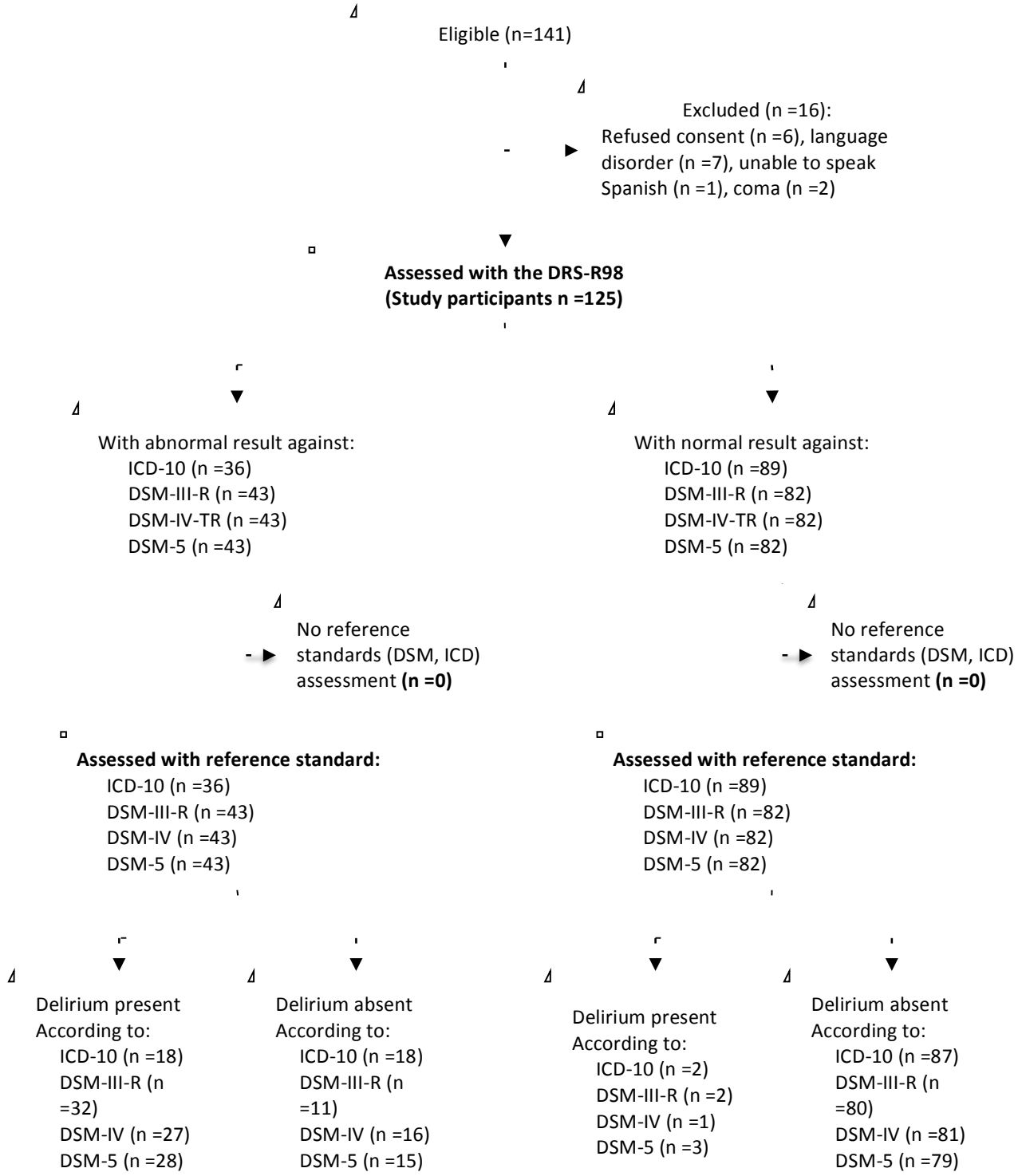


Table 4.1. Demographic and clinical characteristics according to diagnosis groups.
Delirium cases are reported as diagnosed according to DSM-5 diagnostic criteria. Data shown as means ± SD unless denoted by frequencies (percents). Comparisons are between delirium and nondelirium participants.

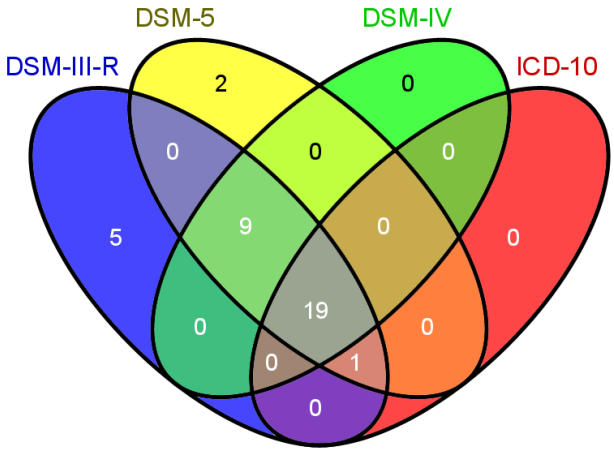
	Whole sample		Subsample with dementia	
Variable	**Nondelirium (n= 94)**	**Delirium (n= 31)**	**Nondelirium (n= 59)**	**Delirium (n= 26)**
Age	77.11±9.16	83.65±6.91*	78.34±7.62	83.42±7.50*
Education (years)	4.93±3.95	4.35±4.44	4.20±3.34	4.19±4.49
Charlson comorbidity score	1.85±1.43	1.97±1.33	2.05±1.43	2.12±1.40
Sex (%)				
Men	44 (46.8)	18 (58.1)	25 (42.4)	15 (57.7)
Women	50 (53.2)	13 (41.9)	34 (57.6)	11 (42.3)
Marital status (%)				
Single	10 (10.6)	4 (12.9)	3 (5.1)	3 (11.5)
Stable partnership	34 (36.2)	16 (51.6)	22 (37.3)	13 (50.0)
Separated / Divorced	9 (9.6)	1 (3.2)	6 (10.2)	1 (3.8)
Widowed	41 (43.6)	10 (32.3)	28 (47.5)	9 (34.6)
Occupational status (%)				
Employed	1 (1.1)	-	1 (1.7)	-
Homemaker	3 (3.2)	-	1 (1.7)	-
Retired	42 (44.7)	21 (67.7)	27 (45.8)	17 (65.4)
Pensioner (other)	46 (48.9)	10 (32.3)	30 (50.8)	9 (34.6)
Unemployed	2 (2.1)	-	-	-
Possible Dementia† (%)	59 (62.8)	26 (83.9)*	N/A	N/A
Medications used‡ (%)				
Anticholinergics	39 (41.5)	15 (48.4)	24 (40.7)	12 (46.2)
Typical Antipsychotics	6 (6.4)	3 (9.7)	5 (8.5)	2 (7.7)
Atypical Antipsychotics	29 (30.9)	17 (54.8)*	24 (40.7)	15 (57.7)
Benzodiazepines	37 (39.4)	16 (51.6)	26 (44.1)	14 (53.8)
Cognitive enhancers	8 (8.5)	1 (3.2)	7 (11.9)	1 (3.8)
Five most common main diagnoses at admission (%)				
Dementia	16 (17.0)	9 (29.0)	15 (25.4)	9 (34.6)
Convalescence for fracture:				
Hip / Femur fracture	13 (13.8)	3 (9.7)	8 (13.6)	3 (11.5)
Other types	10 (10.6)	2 (6.5)	5 (8.5)	1 (3.8)
Psychiatric diagnosis	12 (12.8)	-	11 (18.6)	-*
Cerebrovascular disease	6 (6.4)	6 (19.4)	4 (6.8)	4 (15.4)
Systemic infection	6 (6.4)	5 (16.1)	4 (6.8)	5 (19.2)
Previous diagnosis of delirium§	13 (13.8)	12 (38.7)*	10 (16.9)	10 (38.5)
DRS-R98 Total Score	7.91±7.02	22.48±7.71*	10.78±7.09	22.96±7.72*

* $p < 0.05$.
† S-IQCODE >85.
‡ During 24h before evaluation.
§ As reported in clinical records.
N/A: Not applicable.

4.4.2. Delirium Diagnosis by Classification Systems

The Venn diagram (**Figure 4.2**) shows that 36/125 patients (28.8%) met criteria for delirium by at least one classification system, but only 19/36 (52.8%) met all four criteria which is a low concordance across the classification systems. The most subjects were diagnosed as delirious (27.2%) by DSM-III-R, followed by DSM-5 (24.8%), DSM-IV (22.4%) and ICD-10 (16%). DSM-III-R had the most cases (14.7%) that did not overlap with any other diagnostic classification, yet almost all (34/36) of the delirium cases diagnosed using any system met DSM-III-R criteria showing its inclusiveness. Almost all of the 20/36 ICD-10 delirium cases overlapped with all other systems (19/20).

Figure 4.2. Venn diagram showing overlap for delirium diagnosis.
In 36/125 consecutive patients from a skilled nursing facility, according to four different classifications where 34 (27.2%) patients were diagnosed as delirious according to DSM-III-R, 31 (24.8%) to DSM-5, 28 (22.4%) to DSM-IV and 20 (16%) to ICD-10.



4.4.3. Dementia

Possible preexisting dementia (S-IQCODE score >85) occurred in 85 (68%). There was no difference in age (79.89±7.90 vs. 76.25±10.90, t =-1.894, p =0.063) between those with and without dementia. Those with dementia had more medical comorbidity (CCI-SF score 2.07±1.4 vs. 1.48±1.3; t =-2.245, p =0.027) and more frequent use of atypical antipsychotics (45.9% vs. 17.5%, χ^2 =9.421, p =0.002) than those without dementia.

Dementia patients had a significantly higher occurrence of delirium according to all four diagnostic criteria when compared to those without dementia. Using DSM-5, it was 30.6% vs. 12.5% (χ^2 =4.772, p =0.029), ICD-10 21.2% vs. 5% (χ^2 =5,296, p =0.021), DSM-III-R 35.3% vs. 10% (χ^2 =8.788, p =0.003), and DSM-IV 28.2% vs. 10% (χ^2 =5.203, p =0.023) when comparing dementia vs. nondementia groups.

Table 4.2. Comparison of DRS-R98 individual items (mean ± SD) In 85 hospitalized dementia patients with or without delirium according to different DSM and ICD criteria.

Significant differences at p <0.01 for t tests are bolded.

	DSM-5		ICD-10		DSM-III-R		DSM-IV	
	No delirium (n =59)	**Delirium (n =26)**	**No delirium (n =67)**	**Delirium (n =18)**	**No delirium (n =55)**	**Delirium (n =30)**	**No delirium (n =61)**	**Delirium (n =24)**
DRS-R98 Item								
1. Sleep-wake cycle disturbance	**0.61±0.67**	**1.73±0.67**	**0.72±0.75**	**1.83±0.51**	**0.60±068**	**1.60±0.72**	**0.66±0.70**	**1.71±0.69**
2. Perceptions and hallucinations	0.56±1.10	0.62±1.02	0.55±1.06	0.67±1.03	0.53±1.07	0.67±1.03	0.59±1.10	0.54±0.93
3. Delusions	0.76±1.16	0.38±0.85	0.67±1.12	0.56±0.98	0.80±1.19	0.37±0.81	0.74±1.15	0.42±0.88
4. Lability of affect	0.36±0.55	0.69±0.79	0.37±0.57	0.78±0.81	0.36±0.56	0.63±0.76	0.36±0.55	0.71±0.81
5. Language	**0.54±0.86**	**1.42±1.10**	**0.66±0.95**	**1.39±1.09**	**0.42±0.71**	**1.53±1.11**	**0.54±0.85**	**1.50±1.10**
6. Thought process abnormalities	**0.69±0.81**	**1.46±1.10**	0.82±0.90	1.33±1.14	**0.62±0.73**	**1.50±1.11**	**0.69±0.81**	**1.54±1.10**
7. Motor agitation	**0.36±0.66**	**1.12±0.86**	**0.37±0.67**	**1.39±0.78**	**0.27±0.59**	**1.17±0.83**	**0.36±0.66**	**1.17±0.87**
8. Motor retardation	**0.39±0.69**	**1.50±1.03**	**0.60±0.91**	**1.22±1.00**	**0.42±0.71**	**1.30±1.09**	**0.39±0.69**	**1.58±1.02**
9. Orientation	**1.20±0.89**	**2.15±0.73**	**1.30±0.92**	**2.22±0.65**	**1.11±0.83**	**2.20±0.71**	**1.21±0.88**	**2.21±0.72**
10. Attention	**0.63±0.74**	**2.04±0.87**	**0.79±0.90**	**2.06±0.80**	**0.62±0.73**	**1.87±0.97**	**0.64±0.73**	**2.13±0.85**
11. Short-term memory	**0.41±0.91**	**1.19±1.02**	**0.49±0.94**	**1.22±1.06**	**0.33±0.79**	**1.23±1.10**	**0.43±0.90**	**1.21±1.06**
12. Long-term memory	1.93±1.03	2.50±0.95	**1.93±1.06**	**2.78±0.55**	**1.82±1.06**	**2.63±0.76**	**1.92±1.05**	**2.58±0.83**
13. Visuospatial ability	**0.86±1.02**	**2.15±1.08**	**1.00±1.13**	**2.22±0.94**	**0.73±0.93**	**2.23±1.01**	**0.85±1.01**	**2.29±1.00**
14. Temporal onset of symptoms	**0.64±0.74**	**1.50±0.71**	**0.72±0.75**	**1.61±0.70**	**0.65±0.75**	**1.37±0.76**	**0.66±0.73**	**1.54±0.72**
15. Fluctuation of symptom severity	**0.22±0.46**	**1.00±0.49**	**0.28±0.49**	**1.11±0.47**	**0.20±0.45**	**0.93±0.52**	**0.25±0.47**	**1.00±0.51**
16. Physical disorder	**0.61±0.74**	**1.50±0.58**	**0.70±0.78**	**1.56±0.51**	**0.60±0.76**	**1.40±0.62**	**0.62±0.73**	**1.54±0.59**
DRS-R98 Total score	**10.78±7.09**	**22.96±7.72**	**11.97±8.03**	**23.94±6.81**	**10.07±6.55**	**22.63±7.67**	**10.90±7.03**	**23.67±7.55**

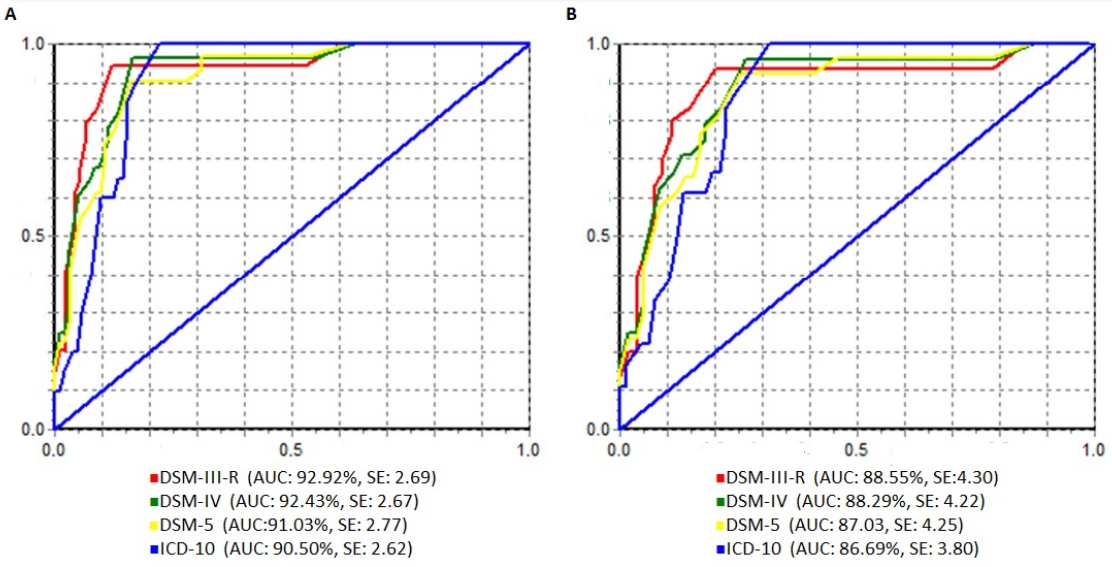
4.4.4. DRS-R98 scores

Mean DRS-R98 Total score for DSM-5 was 22.48±7.71 (range 5-38) in the delirium vs. 7.91±7.02 (range 0-30) in nondelirium group. Similarly, for ICD-10, mean DRS-R98 Total was 23.75±6.60 (range 15-38) vs. 9.20±8.18 (range 0-32); for DSM-III-R, 22.62±7.52 (range 5-38) vs. 7.38±6.44 (range 0-30); and for DSM-IV, 23.50±7.39 (range 5-38) vs. 8.07±6.99 (range 0-30).

There were significant differences ($p \leq 0.01$) in mean values of almost all DRS-R98 items (except for items #2 and 3 representing psychosis), for DRS-R98 Total scores, and in Severity scale scores between subjects with and without delirium according to all diagnostic systems in the whole sample (data not shown). **Table 4.2** shows mean values for DRS-R98 items and Total scale scores for groups with and without delirium in the dementia subsample. Items evaluating the three core domains of delirium had higher mean scores in dementia patients with delirium than nondelirium, but no differences for non-core psychotic and affective items. Mean scores for items representing the circadian domain (sleep-wake cycle, motor disturbances), higher level thinking (language, thought process), and the cognitive domain (attention, visuospatial ability, orientation, memory) as well as diagnostic characteristics (temporal onset, fluctuation, presence of a medical cause) generally had high significance ($p < 0.01$) irrespective of the delirium diagnostic criteria used.

Figure 4.3. ROC curves for the diagnosis of delirium using the DRS-R98 Total scale vs. four different diagnostic criteria of delirium.

A: in the whole sample of 125 subjects admitted to a skilled nursing facility. **B:** in the subsample of 85 patients with dementia (SIQCODE >85). X axes represents 1-Epecificity and Y axes represents Sensitivity, diagonal blue lines denotes 50% of AUC. All p values are >0.05.



4.4.5. ROC Analyses Using DRS-R98

ROC curve analysis (**Figure 4.3**) showed very good discriminant capacity using AUC for the DRS-R98 Total scale for delirium diagnosed using all four systems. AUC was highest for DSM-III-R (92.92%) followed by DSM-IV, DSM-5 and ICD-10, but there was no statistical difference for AUC among them, whether tested for the whole sample or the dementia subsample.

Sensitivity and specificity values for various cut-off scores of the DRS-R98 Total scale are shown for the whole sample in **Table 4.3** and for dementia subsample in **Table 4.4**. Selected highest values that balanced sensitivity and specificity for each criteria system are shown in shaded rows. Best cut-off score for the DRS-R98 Total was ≥14.5 for all systems except ICD-10 (≥15.5), for both all subjects and the subsample.

Table 4.3. Sensitivity and specificity for delirium diagnosis of the DRS-R98 Total scale.
According to each diagnostic classification criteria for 125 consecutive patients admitted to a skilled nursing facility. Shaded areas correspond to the best cut-off scores sensibility and specificity values, for each diagnostic system.

	DSM-5 Criteria		ICD-10 Criteria		DSM-III-R Criteria		DSM-IV Criteria	
Cut-off	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
4.50	100	38.3	100	34.3	100	39.6	100	37.1
5.50	96.8	46.8	100	42.9	94.1	47.3	96.4	45.4
6.50	96.8	58.5	100	53.3	94.1	59.3	96.4	56.7
7.50	96.8	61.7	100	56.2	94.1	62.6	96.4	59.8
8.50	96.8	68.1	100	61.9	94.1	69.2	96.4	66.0
9.50	96.8	69.1	100	62.9	94.1	70.3	96.4	67.0
10.50	93.5	69.1	100	63.8	94.1	71.4	96.4	68.0
11.50	90.3	72.3	100	67.6	94.1	75.8	96.4	72.2
12.50	90.3	74.5	100	69.5	94.1	78.0	96.4	74.2
13.50	90.3	79.8	100	74.3	94.1	83.5	96.4	79.4
14.50	90.3	84.0	100	78.1	94.1	87.9	96.4	83.5
15.50	77.4	87.2	90.0	82.9	82.4	91.2	82.1	86.6
16.50	74.2	89.4	85.0	84.8	79.4	93.4	78.6	88.7
17.50	71.0	89.4	80.0	84.8	76.5	93.4	75.0	88.7
18.50	61.3	90.4	65.0	85,7	67.6	94.5	67.9	90.7
19.50	61.3	91.5	65.0	86.7	64.7	94.5	67.9	91.8
20.50	58.1	92.6	60.0	87.6	61.8	95.6	64.3	92.8
22.50	54.8	94.7	60.0	90.5	52.9	95.6	60.7	94.8
24.50	48.4	95.7	50.0	91.4	47.1	96.7	53.6	95.9
25.50	41.9	96.8	40.0	92.4	41.2	97.8	46.4	96.9
26.50	29.0	96.8	30.0	94.3	29.4	97.8	32.1	96.9
27.50	22.6	97.9	20.0	95.2	20.6	97.8	25.0	97.9
29.00	22.6	98.9	20.0	96.2	20.6	98.9	25.0	99.0
30.50	16.1	100	15.0	98.1	14.7	100	17.9	100
31.50	9.7	100	10.0	99.0	8.8	100	10.7	100
33.50	6.5	100	10.0	100	5.9	100	7.1	100

Using these best DRS-R98 cut-offs from ROC analysis in the whole sample, sensitivity values from highest to lowest were: DSM-IV, DSM-III-R, DSM-5 and ICD-10. Similarly, specificity values were ranked from highest to lowest as DSM-III-R, DSM-5, DSM-IV, and then ICD-10. In the subsample of patients with dementia the order from higher to lower sensitivity at the best cut-offs from ROC analysis was DSM-IV, DSM-III-R, DSM-5 and ICD-10, and the order from higher to lower specificity was DSM-III-R, ICD-10 and DSM-5 with the same score, and DSM-IV. If we use 14.5 as the cut-off score for ICD-10, as for the other criteria, sensitivity increased up to 100% but specificity worsens.

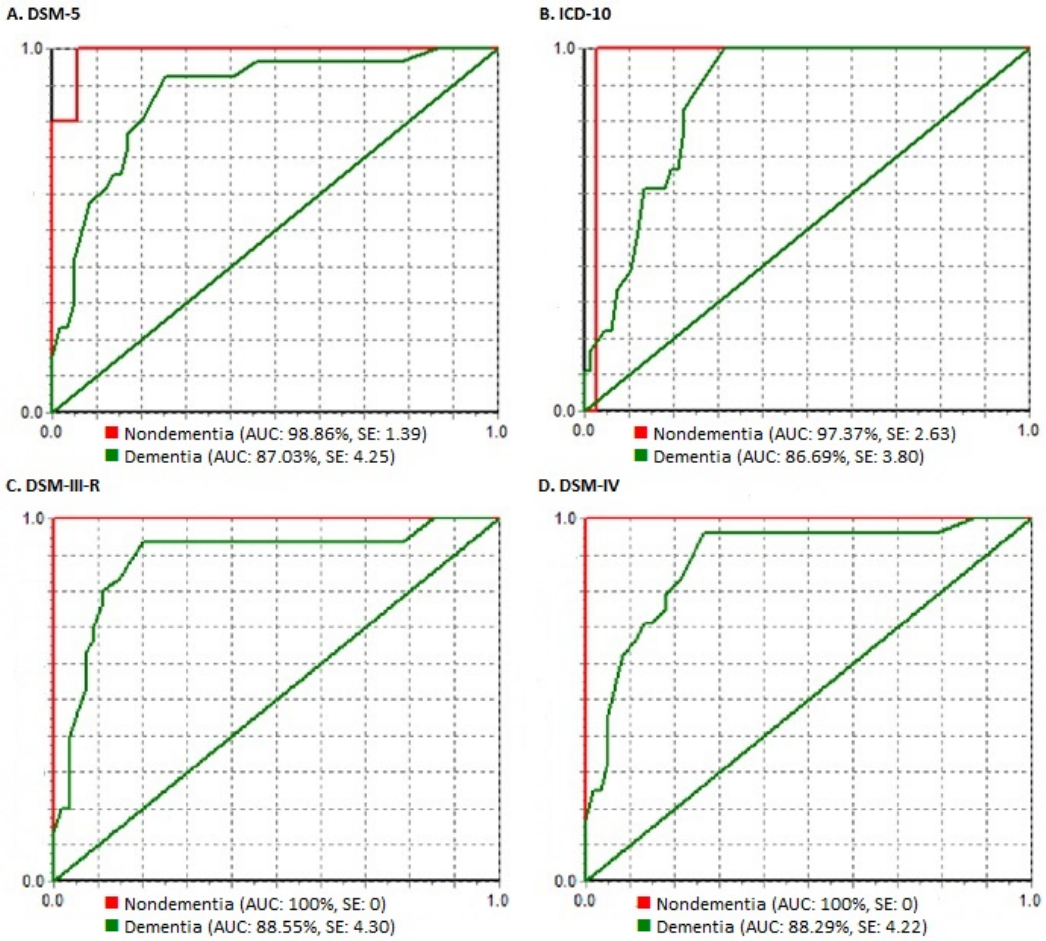
Table 4.4. Sensitivity and specificity for delirium diagnosis of the DRS-R98 Total scale, according to each diagnostic classification criteria, for the subsample of 85 patients with dementia (S-IQCODE >85).
From a skilled nursing facility. Shaded areas correspond to the best cut-off scores sensibility and specificity values, for each diagnostic system.

	DSM-5		ICD-10		DSM-III-R		DSM-IV	
Cut-off	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
4.50	100	13.6	100	11.9	100	14.5	100	13.1
5.50	96.2	22.0	100	20.9	93.3	21.8	95.8	21.3
6.50	96.2	40.7	100	37.3	93.3	41.8	95.8	39.3
7.50	96.2	45.8	100	41.8	93.3	47.3	95.8	44.3
9.50	96.2	54.2	100	49.3	93.3	56.4	95.8	52.5
11.50	92.3	59.3	100	55.2	93.3	63.6	95.8	59.0
12.50	92.3	61.0	100	56.7	93.3	65.5	95.8	60.7
13.50	92.3	69.5	100	64.2	93.3	74.5	95.8	68.9
14.50	92.3	74.6	100	68.7	93.3	80.0	95.8	73.8
15.50	80.8	79.7	88.9	74.6	83.3	85.5	83.3	78.7
16.50	76.9	83.1	83.3	77.6	80.0	89.1	79.2	82.0
17.50	73.1	83.1	77.8	77.6	76.7	89.1	75.0	82.0
18.50	65.4	84.7	66.7	79.1	70.0	90.9	70.8	85.2
19.50	65.4	86.4	66.7	80.6	66.7	90.9	70.8	86.9
20.50	61.5	88.1	61.1	82.1	63.3	92.7	66.7	88.5
22.50	57.7	91.5	61.1	86.6	53.3	92.7	62.5	91.8
24.50	50.0	93.2	50.0	88.1	46.7	95.5	54.2	93.4
25.50	42.3	94.9	38.9	89.6	40.0	96.4	45.8	95.1
26.50	30.8	94.9	33.3	92.5	30.0	96.4	33.3	95.1
27.50	23.1	96.6	22.2	94.0	20.0	96.4	25.0	96.7
29.00	23.1	98.3	22.2	95.5	20.0	98.2	25.0	98.4
30.50	15.4	100	16.7	98.5	13.3	100	16.7	100
31.50	11.5	100	11.1	98.5	10.0	100	12.5	100
33.50	7.7	100	11.1	100	6.7	100	8.3	100

Figure 4.4 compares DRS-R98 Total AUC between groups with and without dementia. The discriminant capacity of the tool was lower in the dementia subsample than in the whole sample, irrespective of the diagnostic criteria used ($p < 0.03$ for all Hanley & McNeil tests χ^2). Similar findings were found for the DRS-

R98 Severity scale (not shown in the figure, p >0.02 for all Hanley & McNeil tests χ^2).

Figure 4.4. Comparison of ROC curves for DRS-R98 Total Scale.
In 85 patients with dementia (SIQCODE >85, green ROC curves) and 40 patients without dementia (reed ROC curves), for each one of the four diagnostic criteria of delirium applied nursing home facility patients. X axes represents 1-Epecificity and Y axes represents Sensitivity, diagonal green lines denotes 50% of AUC. All p values are <0.03.



4.5. Discussion

We present new data on performance of the DRS-R98 when evaluated against four major delirium diagnostic systems in subjects admitted to a skilled nursing facility that had a high prevalence of preexisting dementia. There was poor concordance for delirium diagnosis among the criteria systems. Despite this, the DRS-R98 scale had high discriminant capacity for delirium diagnosis irrespective of the classification system. Using ROC analyses, AUCs for delirium diagnosis ranged from 90.5% (ICD-10) to 92.9% (DSM-III-R) for the whole sample and were somewhat lower for the dementia subsample where AUCs ranged from 86.7% (ICD-10) to 88.5% (DSM-III-R). Balancing sensitivity and specificity values for each diagnostic system to determine the best DRS-R98 cutoff value, all DSM criteria versions had

the same value (≥14.5), while the cutoff for ICD-10 was slightly higher (≥15.5). DRS-R98 showed higher sensitivity for DSM criteria than for ICD-10 at the recommended cut-offs, with DSM-IV having the highest, followed by DSM-III-R, and the new DSM-5. Specificity was higher using DSM-III-R followed by DSM-5, DSM-IV, and ICD-10 with almost the same value for those three.

According to Kendler (2009), inclusion of both current and historical delirium criteria in our analysis is important because a defining feature of a mature science is its cumulative nature and capacity to build on what has gone before. In this sense, evolution of psychiatric criteria could be understood as an iterative process that should increase quality of clinical diagnosis [44]. So, lessons can be learned from quantifying concordance among the evolving delirium criteria and analyzing against them the performance of a tool like DRS-R98 that assesses the wide range of core and non-core phenomenological characteristics of the syndrome.

There was a strikingly low concordance for identification of delirium subjects by all four approaches (around 50%). The phenomenological breadth and depth of criteria varies considerably, with DSM-III-R involving more symptoms than either DSM-IV or DSM-5 that were designed to be less restrictive. The number of delirium cases identified individually by each system also varied considerably (20 for ICD-10, 28 for DSM-IV, 31 for DSM-5, and 34 for DSM-III-R) with the ICD-10 being most restrictive (see Venn diagram in Figure 2). Therefore, one major challenge in evaluating the performance of the DRS-R98 – or any tool for that matter – against a gold standard is when the diagnostic criteria vary so much across the DSM and ICD systems when applied to a given person that one must question which, if any, are truly a gold standard. Certainly we have learned in the field of Alzheimer's dementia that using clinical or research diagnostic criteria is not well validated to neuropathological diagnosis on autopsy [219], thereby making any clinical diagnosis-based standard less than "golden." This is probably the case in delirium where we need biomarker validation in conjunction with the clinical criteria to ascertain true cases. Biomarker research in delirium is lagging though an electrophysiological approach may have the best chance of success were it available in a portable method.

In line with previous studies [25,33,36], we found ICD-10 had the least inclusive criteria due to its requirements for more detailed symptoms though it still does not evaluate all 3 core domains of delirium [51,54,57]. In fact, the high DRS-R98 mean scores of almost 24 in delirium and around 9 in nondelirium according to ICD-10 suggests it captures more full syndromal delirium and fewer subsyndromal cases than do the DSM systems. DSM-III-R diagnosed more patients in our study, even though it incorporates more symptoms than the DSM-IV, similar to the report of Laurila et al. (2003) who found DSM-III-R more inclusive in nursing home patients [33]. On the other hand, DRS-R98 had the highest specificity when compared to DSM-III-R criteria, so it could also be possible that the greater inclusiveness of DSM-III-R better approximates the true prevalence of delirium and could be attributable to its inclusion (though not all required) of symptoms from all three delirium core domains, in particular circadian disturbances of sleep-wake cycle and motor activity and disorganized thinking. Other classifications rely on attention deficits and omit or do not require many symptoms that are considered

core for the syndrome [25,48,51,54,57]. Because of the breadth of types of symptoms that can occur in delirium, it might be that even a more comprehensive listing of symptoms in DSM-5 could enhance the possibility of diagnosis.

The best cut-off values for the DRS-R98 when assessing DSM criteria (14.5) are the same as those reported in the validation against DSM-IV of the Japanese version [132] and relatively similar to those of the Chinese version vs. DSM-IV (15.5)[131] though the Colombian version vs. DSM-IV was a little lower (12.0)[129]. Our values are lower than those in the original English version against DSM-IV (17.75) [45], Portuguese version vs. DSM-IV (20.1)[130], and Korean version vs. DSM-IV (18.5–19.5) [133] validation studies. Differences among studies in cut-off scores could be a consequence of differences in socio-demographical and clinical characteristics of the sample.

We chose the study sample from a skilled nursing facility, and to have a high comorbidity of dementia because this is a challenge to clinicians in diagnosing delirium. Specific DRS-R98 items representing the three core delirium domains, as well as diagnostic characteristics, particularly distinguished delirium in the subgroup of dementia patients. More research is needed as to whether clinicians can rely on those features to detect delirium in dementia patients.

Strengths of this study include independent research ratings for classification systems checklists, and DRS-R98. We used medical records, history-taking, family/carer interview and IQCODE to diagnose pre-existing dementia though this is less rigorous than a complete dementia evaluation. We also did not specify the type of dementia or its severity. Because different types of dementia (e.g. Alzheimer's, vascular, Lewy Body, Frontotemporal) have their own phenomenological patterns, the detection using a delirium-designed tool (DRS-R98) may have been affected somewhat, including our finding of higher mean DRS-R98 Total scores in the nondelirium cases with dementia than in the whole sample that included nondementia patients, suggesting dementia symptoms contribute to the scale scores in a fashion that could reduce the scales' ability to discriminate. Nonetheless, the ROC analyses were similar irrespective of presence of dementia or not; moreover, DRS-R98 items evaluating diagnostic characteristics and symptoms from delirium core domains showed differentiation of delirium from non-delirium among patients with dementia.

In summary, DRS-R98 proved to be a valid and useful instrument for assessing/discriminating delirium in post-acute elderly patients in the skilled nursing home setting, regardless of the inclusiveness of diagnostic system used. Furthermore, it proved to be a valid tool to diagnose delirium in patients with a previous dementia, where the performance of diagnostic criteria is lower. Besides consideration of biomarkers, further evolution of delirium diagnostic criteria should take into account symptoms representing the three core domains so that delirium could be assessed in a more specific way in order to better distinguish full syndromal from subsyndromal and nondelirium cases even in those with dementia
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UNIVERSITAT ROVIRA I VIRGILI
PHENOMENOLOGY AND DIAGNOSTIC CRITERIA FOR DELIRIUM AND SUBSYNDROMAL DELIRIUM IN A POPULATION WITH HIGH PREVALENCE OF DEMENTIA. AN EMPIRICAL STUDY.
Esteban Sepúlveda Ramos

5. Study 2.

Delirium Diagnosis Defined by Cluster Analysis of Symptoms versus Diagnosis by DSM and ICD Criteria: Diagnostic Accuracy Study

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Published in: BMC Psychiatry (2016) 16:167. DOI 10.1186/s12888-016-0878-6

5.1. Aims

- To evaluate the accuracy of the five delirium diagnostic criteria against delirium/nondelirium groups created through cluster analysis of DRS-R98 items.
- To measure the inter-rater reliability of the five diagnostic criteria between two professionals from different disciplines.

5.2. Hypothesis

- The natural aggregation of DRS-R98 items clearly form two groups of subjects corresponding to delirium vs. non-delirium.
- Accuracy of the diagnostic criteria diminishes with the evolution of DSM editions (i.e. from DSM-III-R to DSM-5).
- Inter-rater reliability of DSM editions improves with the evolution of them, as intended by their work teams.
- ICD-10 has low accuracy and inter-rater reliability compared with its DSM counterparts.
- Accuracy and inter-rater reliability for all diagnostic criteria obtain lower values in the demented sample of subjects.

5.3. Methods

5.3.1. Subjects

This is a cross-sectional prospective study of 200 consecutive patients admitted to a skilled nursing facility (Centro Sociosanitario Monterols, Tarragona, Spain). Patients were admitted from home, general hospital, assisted living or senior community for convalescence of medical-surgical conditions or control of geriatric conditions. Exclusion criteria were refusal to participate, coma/sedation, severe language disorder, or inability to speak Spanish.

5.3.2. Ethics, Consent and Permissions

This study was performed in accordance to Declaration of Helsinki and approved by the Hospital Universitari de Sant Joan Ethics Committee (our corresponding evaluation center). All patients or their proxy, when Mini Mental State Examination (MMSE) score was <24 (taken as part of the initial evaluation at admission), gave their written consent to participate.

5.3.3. Measures and Instruments

Demographical and clinical data, including age, sex, marital and occupational status and years of education were collected. We also reviewed medical records for a recent diagnosis of delirium.

Charlson Comorbidity Index (Short form; CCI-SF)
Developed from the CCI with similar prognostic value [216], this version is based on history of 8 medical conditions: cerebrovascular accident, diabetes mellitus, chronic obstructive pulmonary disease, congestive heart failure, dementia, peripheral arterial disease, chronic renal failure and cancer, scored so that the first six receive 1 point and the last two receive 2 points. A CCI-SF score of 0 or 1 indicates no comorbidity, 2 low comorbidity, and ≥3 high comorbidity.

Spanish-Informant Questionnaire on Cognitive Decline in the Elderly (S-IQCODE)
Structured interview composed by 26 questions about cognitive and functional aspects of the patient during the last five years [220]. It is a valid approach to detect a probable dementia. Scores range from 26 to 130. We used the validated Spanish version with the recommended cut-off >85 for possible dementia [217].

Delirium Rating Scale Revised-98 (DRS-R98)
The DRS-R98 has descriptive anchors for rating the severity levels for each of its items (0 is normal to a maximum of 3) with a maximum scale score of 46 points. It measures severity of many delirium symptoms using phenomenologically anchored descriptions for item ratings and can also diagnose delirium. Its 16 items include 3 diagnostic items comprising the DRS-R98 Total scale where 13/16 items constitute the DRS-R98 Severity scale. The DRS-R98 measures core symptoms

representing the 3 core domains of delirium (cognitive, circadian, higher order thinking) and noncore symptoms (psychotic and affective). It was originally validated using raters blinded to the diagnoses in five diagnostic groups of inpatients [45]. It has been subsequently translated and revalidated in countries outside of the U.S. The appropriate Spanish version was used [126], and the expert rater had ample experience in using the scale in delirium phenomenology studies. The Spanish DRS-R98 had very high inter-rater reliability (intraclass correlation coefficient >0.9 in both Colombian and Spanish samples)[126,129], and excellent validity as shown by the area under the curve >0.9 (Receiver-Operator Characteristic analyses) when discriminating DSM-III-R, DSM-IV, DSM-5 or ICD-10 delirium in a sample of patients from the same facility of this study [221]. The DRS-R98 has been assessed against other neuropsychiatric disorders making it an ideal instrument to assess phenomenology [45,59].

Clinical Diagnostic Criteria
We used four classification systems: the DSM-5, DSM-IV and DSM-III-Revised editions (DSM-5, DSM-IV and DSM-III-R) [19,20,27] and the ICD-10 for research [23]. We designed a diagnostic criteria checklist to systematically rate each item for all diagnostic criteria as present or not in order to ensure their complete evaluation.

5.3.4. Procedures

After running a pilot test with 10 patients (not included in the study sample) to evaluate logistic difficulties and possible problems in using research instruments, all patients admitted to the facility were rated by three researchers from 24 to 48 hours after admission (all evaluations were done within the same 24-hour period). Researchers #1 (psychiatrist trained and experienced in delirium and dementia clinical and research evaluations) and #2 (neuropsychologist experienced in evaluation of delirium and dementia for research purposes) evaluated symptoms for the delirium diagnostic criteria checklist. Researcher #3, a psychiatrist experienced in delirium and dementia research, teaching, clinical assessment, and specifically trained on the DRS-R98, administered the Spanish DRS-R98. Evaluations were made independently by each researcher. Ratings were based on the previous 24h period. Researcher #3 also compiled demographic and clinical information for this report and researchers #1 and #2 contacted the family or caregiver to obtain the S-IQCODE score. All of them had unlimited access to medical/nursing records or reports of any kind and to interview caregivers, and were blinded to information from each other.

5.3.5. Statistical Analysis and Delineation of Study Groups

Data were analyzed using SPSS Statistics 17.0 and a spreadsheet.

Continuous variables are expressed as means ± standard deviation (SD). Chi-square test was used to compare categorical variables (continuity correction was

used when appropriate) and t test for continuous ones. Statistical significance was set at $p<0.05$.

Delineation of study groups without a priori criteria using Cluster Analysis of the DRS-R98

We analyzed DRS-R98 Severity Scale (items 1 to 13) using two-step cluster analysis with Log-likelihood as a measure of "distance" between item scores. This is an exploratory technique that reveals natural groupings within a set of data. It allowed us to automatically calculate the number of natural clusters within the dataset without any *a priori* specification of what that number should be. Schwarz's Bayesian Criterion method was used for clustering (to avoid overfitting of the obtained clusters due to the high number of items). Before cluster analysis, we excluded possible colinearity issues by means of a principal components analysis of the items, where any *Eigenvalue* (i.e., the part of the total variance induced by a factor) close to zero suggests a colinearity problem. We used the Belsley criterion to define "close to zero": values between 30 and 100 for the square root of the ratio between the higher and the lower *Eigenvalue* indicate moderate to strong colinearity problems. We did not find concerning colinearity because the higher *Eigenvalue* was 6.045 and the lower was 0.195 (square root of the ratio =5.567).

Discriminant analysis of DSM and ICD criteria for delirium over study groups

Logistic regressions and crosstabs were used to assess sensitivity, specificity, and percentage of subjects correctly classified by each diagnostic system and their individual criteria, and the corresponding 95.0% confidence intervals (95% CI) are reported. Values are also given for diagnostic systems when each of their individual criteria were excluded. Wald test p value was utilized to define if classification performance percentages against reference groups were significant. All discriminant analyses are for the performance of all diagnostic criteria assessed by Researcher #1 (psychiatrist) against DRS-R98 evaluation from Researcher #3 (psychiatrist). Frequency (percentage) of subjects positive for delirium according to each diagnostic system and for presence of their individual criteria was also assessed.

Inter-rater reliability of DSM and ICD criteria for delirium

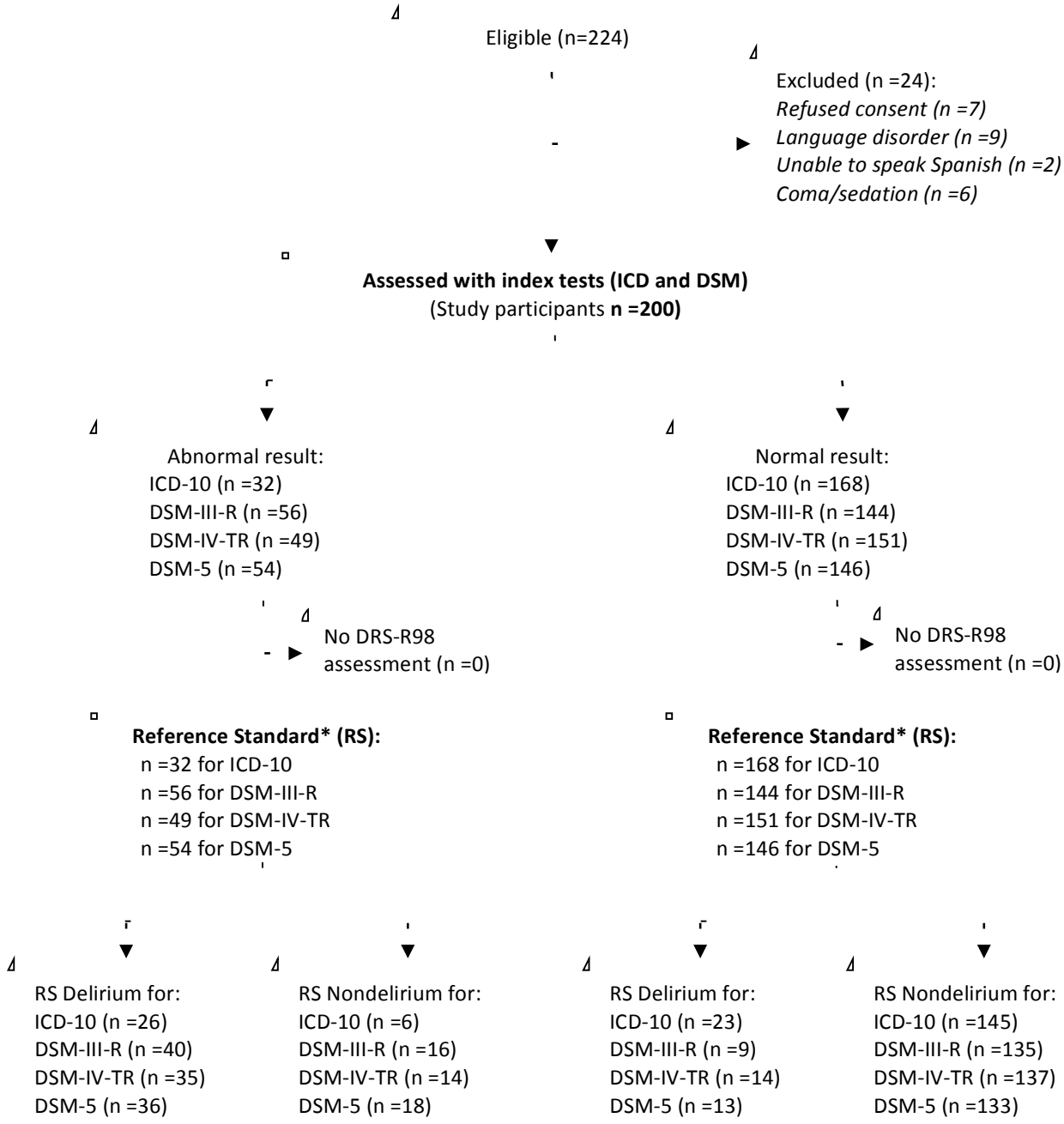
We report Kappa Index (K) with its 95% CI and Standard Error (SE) as measure of reliability of all diagnostic criteria and items (for all diagnostic criteria assessed by Researcher #1 vs. Researcher #2). K for diagnostic systems when each of their individual criteria (items) were excluded is reported also. Every K was interpreted according to the following ranges: <0.20=unacceptable, 0.20-0.39=questionable, 0.4-0.59=acceptable, 0.60-0.79=good, and 0.80-1=excellent.

5.4. Results

Figure 5.1 shows patients flow throughout the study. A total of 224 patients were admitted during the 14 months of patient collection. Reasons for exclusion were denied consent (n =7), severe language disorder (n =9), coma/sedation (n =6),

unable to speak Spanish (n =2), leaving 200 who were included for analyses. Of these, the mean age was 78.3± 9.9 and 51.5% were women.

Figure 5.1. Flow diagram of participants.
Delirium defined by cluster analysis of symptoms vs. diagnosis by DSM and ICD criteria in a sample with high prevalence of dementia.



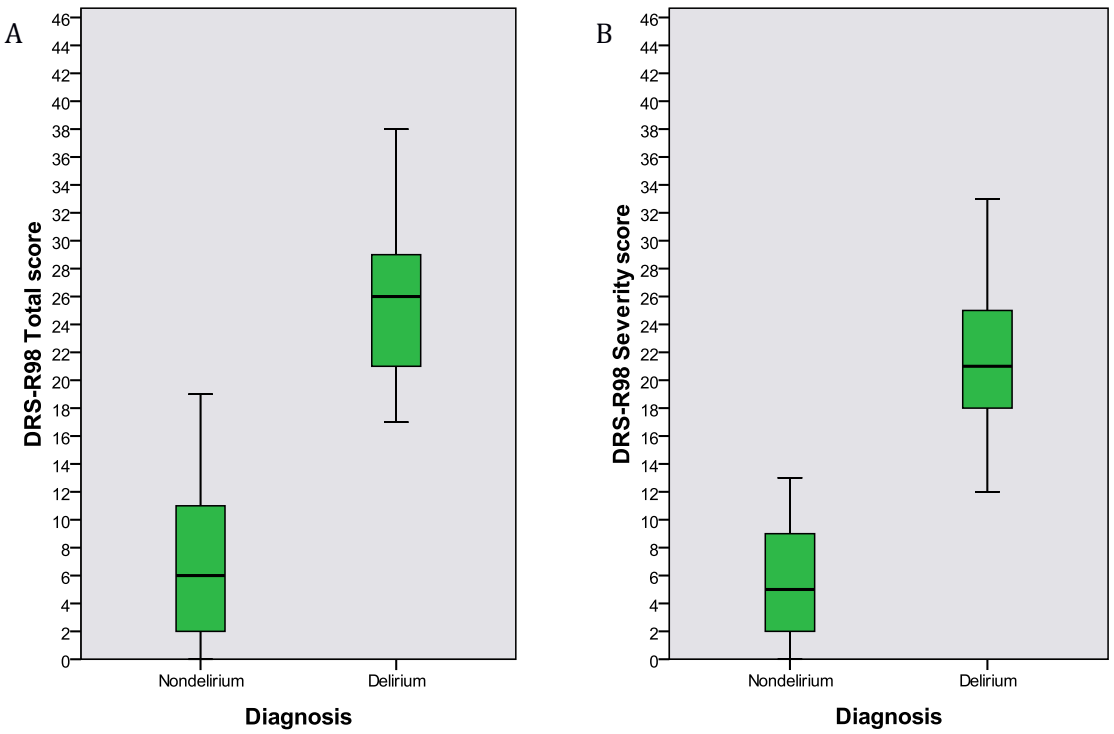
*Assigned to Delirium or Nondelirium "natural" groups by cluster analysis of symptoms assessed with DRS-R98.

5.4.1. Groups Defined According to Cluster Analysis

Cluster analysis of DRS-R98 item scores resulted in a 2-natural cluster (or group) solution (nondelirium n=151, delirium n=49) (Figure 2 boxplots). In nondelirium, the mean score for DRS-R98 Total was 6.67±5.00 (range 0-19) and DRS-R98 Severity was 5.60±3.82 (range 0-13). In delirium, the mean score for DRS-R98 Total was 25.59±4.90 (range 17-38) and DRS-R98 Severity 21.29±4.50 (range 12-33). There was minimal overlap between clusters except for small portions of their tails. Medians were also significantly different (median test p<0.001).

Figure 5.2. Study groups. Boxplots of DRS-R98 to illustrate the two study groups obtained using two-step cluster analysis.

Part A shows distribution of DRS-R98 Total score for the delirium cluster (n =49) and for the nondelirium cluster (n =151). Part B shows DRS-R98 Severity score distribution for the same groups. Solid lines within boxes are median scores; boxes correspond to the middle 50.0% of scores; tails indicate 25thpercentiles.



5.4.2. Population Characteristics

Table 5.1 shows characteristics of the sample, divided into delirium and nondelirium groups using cluster analysis-defined groupings. The delirium group was older, had greater frequency of systemic infection as main diagnosis and a higher frequency of dementia as an antecedent. In both the whole sample and subsample of 117 with dementia (58.5%), delirium subjects were more likely to have a comorbid diagnosis of dementia, and were more often on treatment with

atypical antipsychotics. A past history of delirium was also more common in those with delirium.

Table 5.1. Demographic and clinical characteristics of the sample.
According to cluster analysis-defined delirium and nondelirium status

Variable	Whole sample		Dementia Subsample[a]	
	Nondelirium (n= 151)	Delirium (n= 49)	Nondelirium (n= 76)	Delirium (n= 41)
Age (years)	**77.46 ± 10.30**	**81.06 ± 8.08**	79.62 ± 7.48	81.12 ± 8.22
Education (years)	5.14 ± 4.21	4.61 ± 3.55	3.42 ± 3.32	4.29 ± 3.64
Charlson comorbidity score	1.81 ± 1.54	2.18 ± 1.18	2.07 ± 1.56	2.24 ± 1.18
Sex (%):				
Men	68 (45.0)	29 (59.2)	**26 (34.2)**	**26 (63.4)**
Women	83 (55.0)	20 (40.8)	**50 (65.8)**	**15 (36.6)**
Occupational status (%)				
Employed / Homemaker	6 (4.0)	2 (4.1)	2 (2.6)	1 (2.4)
Retired / Pensioner	143 (94.7)	47 (95.9)	74 (97.4)	40 (97.6)
Unemployed	2 (1.3)	0	-	-
Possible dementia[1] (%)	**76 (50.3)**	**41 (83.7)**	N/A	N/A
Medications used[2] (%):				
Anticholinergics	60 (39.7)	23 (46.9)	30 (39.5)	20 (48.8)
Typical antipsychotics	7 (4.6)	5 (10.2)	4 (5.3)	3 (7.3)
Atypical antipsychotics	**45 (29.8)**	**36 (73.5)**	**29 (38.2)**	**32 (78.0)**
Benzodiazepines	64 (42.4)	20 (40.8)	38 (50.0)	15 (36.6)
Cognitive enhancers	10 (6.6)	5 (10.2)	9 (11.8)	5 (12.2)
Five most common main diagnoses on admission (%)				
Dementia	**14 (9.3)**	**17 (34.7)**	**14 (18.4)**	**17 (41.5)**
Convalescence for fracture:			15 (19.7)	
Hip / Femur fracture	31 (20.5)	5 (10.2)	7 (9.2)	4 (9.8)
Other types	19 (12.6)	3 (6.1)		1 (2.4)
Psychiatric diagnosis	**17 (11.3)**	**-**	**11 (14.5)**	**-**
Cerebrovascular disease	15 (9.9)	7 (14.3)	7 (9.2)	5 (12.2)
Systemic infection	**9 (6.0)**	**8 (16.3)**	5 (6.6)	8 (19.5)
Previous diagnosis of delirium[3]	**18 (11.9)**	**15 (30.6)**	**12 (15.8)**	**13 (31.7)**
DRS-R98 Severity Score	**5.60 ± 3.82**	**21.29 ± 4.50**	**7.47 ± 3.30**	**21.63 ± 4.51**
DRS-R98 Total Score	**6.67 ± 5.00**	**25.99 ± 4.90**	**8.87 ± 4.37**	**25.76 ± 5.00**
DSM-III-R diagnoses (n)	**16 (10.6)**	**40 (81.6)**	**10 (13.1)**	**32 (78.0)**
DSM-IV diagnoses (n)	**14 (9.3)**	**35 (71.4)**	**7 (9.2)**	**27 (65.8)**
DSM-5 diagnoses (n)	**18 (11.9)**	**36 (73.5)**	**10 (13.1)**	**28 (68.3)**
ICD-10 diagnoses (n)	**6 (4.0)**	**26 (53.1)**	**5 (6.6)**	**20 (48.8)**

Data are shown as means ± SD unless denoted by frequencies, which are expressed as n (%). **Bolded values** reached significance at $p < 0.05$ for differences between delirium and nondelirium groups.
[1] Based on S-IQCODE > 85. [2] During 24h before research evaluation. [3] As reported in clinical records.
N/A: Not Applicable.

Delirium and nondelirium cases are listed according to the four diagnostic systems. The higher frequency was for DSM-III-R delirium with 56/200 cases (28.0%), and

the lower was for ICD-10 with 32/200 cases (16.0%); DSM-III-R delirium achieved the higher coincidence percentage with the reference standard delirium, ICD-10 obtained the lower (Table 1). Delirium was significantly more prevalent in the 117 with dementia than in the 83 without dementia for almost all diagnostic criteria: 8.4% delirium in nondementia vs. 21.4% in dementia subjects for ICD-10 (χ^2 =6.043, p =0.014); 19.3% vs. 32.5% for DSM-5 (χ^2 =4.293, p=0.038) and 16.9% vs. 35.9% for DSM-III-R (χ^2 =8.722, p=0.003). There was a similar trend for DSM-IV, with 18.1% vs. 29.1% (χ^2 =3.169, p=0.075).

5.4.3. Criteria Systems Accuracy

Delirium classification performance characteristics for each diagnostic system and their individual criteria are shown in **Table 5.2.** All diagnostic systems correctly classified subjects similarly enough to the cluster-defined groups to be significant (Wald statistic p<0.05). In the whole sample all diagnostic systems had very good accuracy, where the highest percentage of correctly classified cases was obtained by DSM-III-R criteria (87.5%) and followed closely by DSM-IV (86.0%), ICD-10 (85.5%) and DSM-5 (84.5%). The pattern was for all to have lower sensitivity than specificity especially evident for ICD-10 with specificity of 96.0% and the lowest sensitivity of 53.1%. In contrast, DSM-III-R had the best sensitivity (81.6%) and the most balanced sensitivity-specificity values.

All diagnostic systems were relatively robust and, in general terms, maintained their classification performance when each individual criteria was excluded. Each of the individual criteria correctly classified subjects (p<0.05), except for criterion C of DSM-III-R (57.5%) and for criterion C of DSM-5 (47.0%) in the demented subsample. DSM-5 criterion C had significant but low accuracy (51.5%) in the whole sample. These two individual criteria were each compound (listing more than one type of symptom).

The cardinal criterion A from all diagnostic systems (attention) had high accuracies and reasonably well-balanced sensitivity and specificity. Evaluation of other cognitive symptoms obtained high sensitivity (98.0% for ICD-10 and DSM-5), however specificity was very low (ICD-10 =49.0%; DSM-5 =36.4%). DSM-IV was better balanced (criterion B). Only DSM-III-R includes a criterion for disorganized thinking which performed well (89.8% specificity, 78.5% sensitivity), and a separate criterion for motor activity evaluation, which obtained a high sensitivity (95.9%). ICD-10 had criteria for psychomotor disturbance and sleep-wake cycle disturbance, which performed moderately well.

As expected, individual criteria with high sensitivity, as reported in **Table 5.2**, had the highest percentage of positivity for delirium within their corresponding whole sample or dementia subsample (**Supplemental Table 5.1**).

The results for the dementia subsample were similar to the whole sample except that accuracy, sensitivity and specificity were all slightly lower. The largest decrease in accuracy between the whole sample and the dementia subsample was for ICD-10 (from 85.5% to 77.8%). And when excluding an individual criterion, the

largest reduction was for ICD-10 criterion evaluating memory and orientation (from 61.0% to 48.7%).

In the whole sample, the acute onset criteria (86.0-87.0%) and the criteria including attentional disturbance (84.5-88.0%) had the highest classification accuracy within each system. The highest individual criterion accuracy (88.0%) was in ICD-10 for "clouding of consciousness and attention alteration." This same pattern occurred in the dementia subsample though the values were slightly lower – 82.9-84.6% and 80.3-84.6%, respectively, with DSM-III-R performing the worst on each criterion.

5.4.4. Reliability

Reliability of the four diagnostic systems is shown in **Table 5.3**. DSM-IV, DSM-III-R, and ICD-10 showed K values in the range of acceptable to good in the whole sample. DSM-5 did the best with the highest K value and when considering its individual criteria, also had most values in the good range irrespective of which sample was tested. In contrast, DSM-III-R performed the most poorly, with the highest number of questionable range K values in the dementia subsample. The reliability performance of both systems would remain almost the same if any of their individual criteria were excluded. No criterion performed in the unacceptable or excellent range.

Standard errors for each system and their individual criteria were all ≤ 0.1 with exception of the compound criterion C of DSM-III-R (SE 0.129) and the criterion C of DSM-5 for additional cognitive change (SE 0.140) in the subset with dementia.

5.5. Discussion

We describe a novel approach to evaluate how different delirium diagnostic systems perform in their ability to separate delirium and nondelirium groups, given that reliance on any particular diagnostic system *a priori* makes an assumption of superior validity if it is to be used as a reference standard. Instead, we applied cluster analysis of DRS-R98 items to a sample of 200 subjects to discern natural groups as the reference standard and then measured performance of four classification systems to diagnose delirium. The DRS-R98 uses phenomenological descriptive anchors for many delirium characteristics that were assessed in a standardized way, independently and without regard for a particular classification system ("agnostic"). Our DRS-R98 cluster analysis yielded two clearly differentiated groups, which indicates very good performance to serve as a reference standard. Additionally, dementia patients with or without delirium were included to increase diagnostic complexity.

Table 5.2. Classification performance for delirium diagnostic systems and their individual criteria as compared to cluster analysis-defined groups.

Classification Systems and their Criteria	Accuracy in the whole sample (n =200)						Accuracy in dementia subsample (n =117)					
	Sensitivity %	95% CI	Specificity %	95% CI	Accuracy %	95% CI	Sensitivity %	95% CI	Specificity %	95% CI	Accuracy %	95% CI
DSM-III-R	81.6	67.5-90.8	89.4	83.1-93.6	**87.5**	81.9-91.6	78.0	62.0-88.9	86.8	76.7-93.2	**83.8**	75.5-89.7
A Alteration to maintain and shift attention	85.7 [81.6]	72.1-93.6	84.1 [89.4]	77.1-89.4	**84.5 [87.5]**	78.6-89.1	82.9 [78.0]	67.3-92.3	78.9 [86.8]	67.8-87.1	**80.3 [83.8]**	71.8-86.9
B Disorganized thinking	89.8 [81.6]	77.0-96.2	79.5 [87.4]	72.0-85.4	**82.0 [86.0]**	75.8-86.9	87.8 [78.0]	73.0-95.4	68.4 [85.5]	**56.6-78.3**	**75.2 [82.9]**	66.2-82.5
C Alterations in two of: consciousness, perception, sleep – wake cycle, motor activity, orientation and memory.	100 [81.6]	90.9-99.8	43.7 [89.4]	35.7-52.0	57.5 **[87.5]**	50.3-64.4	100 [78.0]	89.3-99.8	18.4 [86.8]	10.8-29.3	47.0 **[83.8]**	37.8-56.4
D Acute onset and fluctuation tendency.	81.6 [83.7]	67.5-90.8	87.4 [88.1]	80.8-92.1	**86.0 [87.0]**	80.2-90.3	78.0 [80.5]	62.0-88.9	85.5 [84.2]	75.1-92.2	**82.9 [82.9]**	74.6-89.0
E Evidenced or presumed etiological cause.	83.7 [81.6]	69.8-92.2	80.8 [89.4]	73.4-86.6	**81.5 [87.5]**	75.3-86.5	80.5 [78.0]	64.6-90.6	78.9 [86.8]	67.8-87.1	**79.5 [83.8]**	70.8-86.2
DSM-IV	71.4	56.5-83.0	90.7	84.6-94.6	**86.0**	80.2-90.3	65.9	49.3-79.4	90.8	81.4-95.9	**82.1**	73.6-88.3
A Disturbance of consciousness and attention	83.7 [73.5]	69.8-92.2	87.4 [88.7]	80.8-92.1	**86.5 [85.0]**	80.8-90.8	80.5 [68.3]	64.6-90.6	84.2 [88.2]	73.6-91.2	**82.9 [81.2]**	74.6-89.0
B Cognition alteration or perceptual disturbance, not explained by a dementia.	83.7 [73.5]	69.8-92.2	80.1 [90.7]	72.7-86.0	**81.0 [86.5]**	74.7-86.0	80.5 [68.3]	64.6-90.6	78.9 [90.8]	67.8-87.1	**79.5 [82.9]**	70.8-86.2
C Acute onset and fluctuation tendency.	83.7 [71.4]	69.8-92.2	88.1 [89.4]	81.6-92.6	**87.0 [85.0]**	81.3-91.2	80.5 [65.9]	64.6-90.6	86.8 [88.2]	76.7-93.2	**84.6 [80.3]**	76.5-90.4
D Evidence for etiology.	75.5 [79.6]	60.8-86.2	81.5 [90.7]	74.1-87.1	**80.0 [88.0]**	73.6-85.2	70.7 [75.6]	54.3-83.3	80.3 [90.8]	69.2-88.2	**76.9 [85.5]**	68.0-84.0
DSM-5	73.5	58.7-84.6	88.1	81.6-92.6	**84.5**	78.6-89.1	68.3	51.8-81.4	86.8	76.7-93.2	**80.3**	71.8-86.9
A Disturbance in attention and awareness.	85.7 [73.5]	72.1-93.6	86.1 [88.1]	79.3-91.0	**86.0 [84.5]**	80.2-90.3	82.9 [68.3]	67.3-92.3	82.9 [86.8]	72.2-90.2	**82.9 [80.3]**	74.6-89.0
B Acute onset and fluctuation tendency.	83.7 [73.5]	69.8-92.2	88.1 [86.8]	81.6-92.6	**87.0 [83.5]**	81.3-91.2	80.5 [68.3]	64.6-90.6	86.8 [84.2]	76.7-93.2	**84.6 [78.6]**	76.5-90.4
C Additional cognitive change or perception disturbance.	98.0 [73.5]	87.8-99.9	36.4 [88.1]	28.9-44.7	**51.5 [84.5]**	44.4-58.6	97.6 [68.3]	85.6-99.9	14.5 [86.8]	7.8-24.8	43.6 **[80.3]**	34.5-53.1
D No better explanation by another neurocognitive disorder nor reduced level of arousal.	81.6 [75.5]	67.5-90.8	84.1 [88.1]	77.1-89.4	**83.5 [85.0]**	77.5-88.2	78.0 [70.7]	62.0-88.9	82.9 [86.8]	72.2-90.2	**81.2 [81.2]**	72.7-87.6

E Evidence for etiology.	75.5 [81.6]	60.8-86.2	81.5 [88.1]	74.1-87.1	**80.0 [86.5]**	73.6-85.2	70.7 [78.0]	54.3-83.3	80.3 [86.8]	69.2-88.2	**76.9 [83.8]**	68.0-84.0
ICD-10	53.1	38.4-67.2	96.0	91.2-98.4	**85.5**	79.7-89.9	48.8	33.1-64.6	93.4	84.7-97.5	**77.8**	**69.0-84.7**
A Clouding of consciousness and attention alteration.	81.6 [55.1]	67.5-90.8	90.1 [94.0]	83.9-94.1	**88.0 [84.5]**	82.5-92.0	78.0 [51.2]	62.0-88.9	88.2 [90.8]	78.2-94.1	**84.6 [76.9]**	76.5-90.4
B Disturbance of cognition (memory and orientation).	98.0 [55.1]	87.8-99.9	49.0 [96.0]	40.8-57.2	**61.0 [86.0]**	53.8-67.7	97.6 [51.2]	85.6-99.9	22.4 [93.4]	13.9-33.6	**48.7 [78.6]**	39.4-58.1
C One psychomotor disturbance (shifts from hypo to hyperactivity, reaction time increased, speech increased /decreased, enhanced startle reaction)	95.9 [53.1]	84.9-99.3	66.2 [96.0]	58.0-73.6	**73.5 [85.5]**	66.7-79.4	95.1 [48.8]	82.2-99.1	57.9 [93.4]	46.0-68.9	**70.9 [77.8]**	61.7-78.8
D Sleep-wake alteration (includes nocturnal worsening and hypnopompic disturbances)	71.4 [67.3]	56.5-83.0	72.2 [92.7]	64.2-79.0	**72.0 [86.5]**	65.1-78.0	70.7 [63.4]	54.3-83.3	61.8 [92.1]	49.9-72.5	**65.0 [82.1]**	55.5-73.4
E Rapid onset and fluctuations.	77.6 [53.1]	63.0-87.7	89.4 [95.4]	83.1-93.6	**86.5 [85.0]**	80.8-90.8	75.6 [48.8]	59.4-87.1	88.2 [92.1]	78.2-94.1	**83.8 [76.9]**	75.5-89.7
F Evidence for an etiologic cause.	77.6 [59.2]	63.0-87.7	80.1 [96.0]	72.7-86.0	**79.5 [87.0]**	73.1-84.7	73.2 [56.1]	56.8-85.2	76.3 [93.4]	64.9-85.0	**75.2 [80.3]**	66.2-82.5

Cluster analysis-defined groups were identified using DRS-R98 items. Performance characteristics and 95% confidence intervals (95% CI) are given for each classification system. Performance values for the diagnostic criteria after each individual criterion was excluded are noted within brackets. Bolded values denote when the percentage of correctly classified cases (accuracy) as compared to the reference standard are significant at $p < 0.05$ according to the Wald test.

Supplemental Table 5.1. Frequency of patients positive for delirium according to each classification system and presence of their individual criteria.
Expressed for the whole sample (where the cluster analysis-defined delirium group was 49/200 patients or 24.5%) and for the dementia subsample (where the cluster analysis-defined delirium group was 41/117, 35.0%).

Diagnostic Criteria	Whole sample (n =200)	Dementia subsample (n =117)
	n (%)	n (%)
DSM-III-R	56 (29.5)	42 (35.9)
A Alteration to maintain and shift attention	66 (33.0)	50 (42.7)
B Disorganized thinking	75 (37.5)	60 (51.3)
C Alterations in two of: consciousness, perception, sleep-wake cycle, motor activity, orientation and memory.	134 (67.0)	103 (88.0)
D Acute onset and fluctuation tendency.	59 (29.5)	43 (36.7)
E Evidenced or presumed etiological cause.	70 (35.0)	49 (41.9)
DSM-IV	49 (24.5)	34 (29.0)
A Disturbance of consciousness and attention	60 (30.0)	45 (38.5)
B Cognition alteration or perceptual disturbance, not explained by a dementia.	71 (35.5)	49 (41.9)
C Acute onset and fluctuation tendency.	59 (29.5)	43 (36.7)
D Evidence for etiology.	65 (32.5)	44 (37.6)
DSM-5	54 (27.0)	38 (32.5)
A Disturbance in attention and awareness.	63 (31.5)	47 (40.2)
B Acute onset and fluctuation tendency.	59 (29.5)	43 (36.7)
C Additional cognitive change or perception disturbance.	144 (72.0)	105 (89.7)
D No better explanation by another neurocognitive disorder nor reduced level of arousal.	64 (32.0)	45 (38.5)
E Evidence for etiology.	65 (32.5)	44 (37.6)
ICD-10	32 (16.0)	25 (21.4)
A Clouding of consciousness and attention alteration.	55 (27.5)	41 (35.0)
B Disturbance of cognition (memory and orientation).	125 (62.5)	99 (84.6)
C One psychomotor disturbance (shifts from hypo to hyperactivity, reaction time increased, speech increased /decreased, enhanced startle reaction)	98 (49.0)	71 (60.7)
D Sleep-wake alteration (includes nocturnal worsening and hypnopompic disturbances)	77 (38.5)	58 (49.6)
E Rapid onset and fluctuations.	54 (27.0)	40 (34.2)
F Evidence for an etiologic cause.	68 (34.0)	48 (41.0)

Accuracy was very good for all diagnostic systems with DSM-III-R the highest (87.5%) and DSM-5 the lowest (84.5%). Overall, the classification performance in the dementia subsample was similar to but somewhat lower than in the whole sample, with ICD-10 performing the least well (77.8%) and DSM-III-R somewhat better (83.8%) than the other DSM versions. Values for sensitivity and specificity varied more than did accuracy in the whole sample, where the pattern for all was lower sensitivity than specificity. The most extreme was ICD-10 (53.1%, 96.0%) suggesting a better capacity for delirium confirmation, while the most balanced values were for DSM-III-R (81.6%, 89.4%). Each individual criterion, except one, significantly distinguished delirium and nondelirium groups in both the whole sample and dementia subsample.

Table 5.3. Reliability between two raters for delirium classification systems and their individual criteria.

Classification Systems and their Criteria	Reliability whole sample (n =200)		Reliability dementia subset (n =117)	
	Kappa	95% CI	Kappa	95% CI
DSM-III-R	**0.62**	0.49-0.75	0.58	0.42-074
A Alteration to maintain and shift attention	**0.61** [0.58]	0.50-0.73	0.48 [0.52]	0.32-0.54
B Disorganized thinking	0.42 **[0.67]**	0.29-0.55	*0.35* **[0.61]**	0.18-0.52
C Alterations in two of: consciousness, perception, sleep – wake cycle, motor activity, orientation and memory.	**0.66** **[0.61]**	0.55-0.77	*0.29* [0.57]	-0.02-0.60
D Acute onset and fluctuation tendency.	0.58 **[0.62]**	0.46-0.70	0.51 [0.58]	0.35-0.67
E Evidenced or presumed etiological cause.	0.45 **[0.62]**	0.33-0.57	*0.35* [0.58]	0.18-0.51
DSM-IV	**0.63**	0.50-0.76	0.54	0.37-0.72
A Disturbance of consciousness and attention	0.59 [0.56]	0.47-0.71	0.45 [0.47]	0.29-0.61
B Cognition alteration or perceptual disturbance, not explained by a dementia.	0.43 **[0.66]**	0.31-0.56	*0.31* [0.59]	0.15-0.48
C Acute onset and fluctuation tendency.	**0.61** **[0.63]**	0.49-0.73	0.54 [0.53]	0.39-0.70
D Evidence for etiology.	0.57 **[0.64]**	0.46-0.68	0.47 [0.56]	0.31-0.62
DSM-5	**0.73**	0.62-0.84	**0.67**	0.53-0.82
A Disturbance in attention and awareness.	**0.67** **[0.73]**	0.56-0.78	0.57 **[0.67]**	0.42-0.71
B Acute onset and fluctuation tendency.	**0.71** **[0.71]**	0.60-0.81	**0.63** **[0.65]**	0.48-0.77
C Additional cognitive change or perception disturbance.	0.47 **[0.73]**	0.33-0.62	*0.30* **[0.67]**	-0.5-0.64
D No better explanation by another neurocognitive disorder nor reduced level of arousal.	**0.68** **[0.70]**	0.57-0.79	**0.61** **[0.62]**	0.49-0.76
E Evidence for etiology.	0.58 **[0.72]**	0.47-0.69	0.46 **[0.65]**	0.31-0.61
ICD-10	0.57	0.42-0.73	0.49	0.29-0.68
A Clouding of consciousness and attention alteration.	0.58 [0.59]	0.45-0.70	0.45 [0.52]	0.29-0.61
B Disturbance of cognition (memory and orientation).	**0.69** [0.59]	0.59-0.79	0.52 [0.54]	0.32-0.72
C One psychomotor disturbance (shifts from hypo to hyperactivity, reaction time increased, speech increased /decreased, enhanced startle reaction)	0.52 [0.55]	0.40-0.64	0.49 [0.45]	0.32-0.65
D One alteration of sleep – wake (insomnia, nocturnal worsening, nightmares)	0.52 [0.56]	0.40-0.64	0.49 [0.52]	0.33-0.65
E Rapid onset and fluctuations.	0.58 [0.54]	0.45-0.71	0.50 [0.49]	0.34-0.66
F Evidence for an etiologic cause.	0.50 [0.57]	0.39-0.62	*0.37* [0.47]	0.21-0.53

Kappa for each classification system if each individual criterion were excluded is within brackets. Values in the questionable or unacceptable ranges are italicized. Values in the good range are bolded. K: <0.20=unacceptable, 0.20-0.39=questionable, 0.40-0.59=acceptable, 0.60-0.79=good, and 0.80-1=excellent

Accuracies of diagnostic criteria remained robust even after each individual criterion was excluded such that they perform as an integrated whole. Exclusion of most of the individual criteria resulted in only small increases in classification accuracy of the remaining criteria. However, several individual criteria reduced overall classification accuracy before they were excluded and the most prominent of these had a compound construction (more than one type of symptom listed together). Inter-rater reliability for diagnostic systems was "good" except for ICD-10 that was "acceptable", but none were excellent. ICD-10 had the lowest and DSM-5 had the highest interrater reliability.

The individual criteria across all classification systems with the highest accuracies were those for attentional disturbance and acute onset of symptoms, consistent with inattention being a cardinal feature and the syndrome being a noticeable change in consciousness. These might comprise the simplest screening approach for busy clinicians but has not been studied. Meagher at al. [59] reported that digit span forwards differentiated delirium from dementia subjects because simple inattention occurs in delirium more than in dementia, whereas both groups performed poorly on the more challenging backwards span test. A commonly used brief tool, the CAM [61], includes both inattention and acute onset among its four items, however, it does not have consistent concordance with DSM versions and DRS-R98 [39,40].

These diagnostic systems varied greatly as to how many of the other cognitive, perceptual, thinking and circadian symptoms of delirium are represented. Interestingly the disorganized thinking criterion of DSM-IIIR performed well. However, the disorganized thinking was dropped as a criterion after DSM-III-R in order to improve the reliability of delirium diagnosis when assessed by non-psychiatrists [34]. However, as a core domain symptom our data suggest it should be included again in diagnostic criteria. Two other core domain symptoms, that describe circadian activity, have separate criteria in ICD-10 but performed only moderately well in accuracy. However, they performed better than the "other cognitive" criterion in ICD-10.

None of these four diagnostic systems has individual criteria representing all three core domains of delirium (cognitive, circadian, and higher order thinking) [19,20,23,27]. DSM-III-R has disorganized thinking and ICD-10 has two circadian criteria. DSM-III-R includes more core domain symptoms than do the other DSM versions, though they are collapsed with "consciousness" into one compound criterion (i.e., consciousness, perception, sleep-wake cycle, motor activity, orientation and memory). This particular compound criterion was the only criterion from among all the systems whose accuracy was not significantly different between delirium and nondelirium groups. It would be worth studying new criteria that individually capture all three core domains.

Further, the compound criteria from DSM-III-R (C), DSM-IV (B), and DSM-5 (C) each carried lower accuracy contributions than when they were deleted. Because compound criteria, comprised of more than one type of symptom, had lower accuracies we recommend they be avoided in future diagnostic system revisions.

Accuracies were highest for the A criteria in each system, consistent with their being cardinal for the syndrome of delirium. Though other symptoms besides inattention had lower accuracies, such as evaluating other cognitive aspects, they showed high sensitivity despite low specificity. As such, they may be useful for delirium screening.

The wording of the cardinal A criterion varies across these systems, where DSM-IV and ICD-10 include mention "consciousness" along with inattention. Though contributing much to accuracy, interrater reliability was less strong when inattention was combined with consciousness as compared to cardinal criteria that only included the components of consciousness (i.e., attention and awareness). "Clouding of consciousness" has no precise or common definition however. Note that the DRS-R98 does not include vague items like "consciousness" or "clouding of consciousness." Rather, the symptoms of delirium taken together should represent the components of an impairment of consciousness, where cerebral cortical arousal is intact (i.e., level of consciousness is not coma or stupor). Intact consciousness means being alert/attentive (and having other cognitive domains intact), awake (with an intact sleep-wake cycle), and aware (comprehending one's inner self and one's surroundings). So to include the term consciousness within the criteria is not helpful to delineate the particular features of delirium that would establish it as an impaired state of consciousness by its overall definition [40]. Thus, the raters would be influenced by their overall impression of the patient's presentation during the interview to rate consciousness, similar to a clinical global impressions scale (CGI). DRS-R98 items do not include "consciousness" terms and can more cleanly establish the components of delirium when cluster analysis determined the groups. Because we found the highest accuracy (88.0%) for the ICD-10 "clouding of consciousness and attention alteration" cardinal A criterion, it suggests that such wording functioned like a CGI rating and could be a candidate for a single screening question for use by clinicians in hospital settings.

Cognitive alterations are core for both dementia and delirium, and symptoms of the latter overshadow those of the former when they are comorbid [54,59,120], which may explain the decreased accuracy performance of diagnostic systems within the dementia subsample. Classification performance for all diagnostic systems in that subsample was slightly lower than in the whole sample, but over 80.0% accuracy for all except ICD-10 that suffered the largest decline (7.7 percentage points). The ICD-10 criterion evaluating memory and orientation also had the highest accuracy drop within ICD-10 and among all individual criteria (12.3 percentage points) suggesting ICD-10 may not be as suitable for use in comorbid dementia cases though this needs confirmation in other studies.

Inter-rater reliability was highest for DSM-5 and, in the dementia subsample, the lowest for DSM-III-R when considering individual criteria reliabilities. Similar to a previous report of low ICD-10 reliability in general hospital inpatients, we found ICD-10 criteria had the worst reliability values [43]. Reliability values were somewhat lower in the dementia subsample overall as compared with the whole sample. As suggested by Regier et al. [32], comorbidity is usually associated with lower reliability values, especially when concurrent entities have shared symptoms, as happens with dementia and delirium. It could explain why although

all diagnostic systems and individual criteria were very precise (95% CI <0.5 and SE < 0.1) in the whole sample, criteria that included cognitive aspects of delirium (criterion C in DSM-III-R and DSM-5) had SE a little over the desired 0.1 value in the subsample with dementia.

Though DSM-5 criteria had the best reliability, its accuracy in our sample was a little lower than the other systems, whereas DSM-III-R had the highest accuracy of 87.5%. A previous report using latent class analysis found that DSM-III-R had higher accuracy than DSM-IV [36]. These findings, taken together, may be a consequence of the trend toward simplification of criteria over newer DSM editions which improve reliability at the expense of lowering accuracy. An alternative to oversimplification to enhance reliability for nonspecialists is to include operational descriptions for each criterion in future DSM versions, similar to what is available for the DRS-R98 Administration Guide (pdf available from Dr. Trzepacz at pttrzepacz@outlook.com).

Limitations include our use of only the DRS-R98 to capture characteristics of delirium. Designed for broad and detailed phenomenological descriptions of delirium features, it is ideal for this study's purpose with advantages over other existing assessment tools that are not so structured. A reliable yet-to-be-determined biological marker, perhaps electroencephalography or fMRI, would be an important addition to phenotype criteria validity assessment, which we did not include.

5.6. Conclusions

All diagnostic systems classified (>80.0%) delirium from nondelirium cases as compared to an agnostic cluster-analysis reference standard, though all performed less well in the comorbid dementia subsample. The two best performing individual criteria across all classification systems were the attentional disturbance and acute onset features. Compound criteria (i.e., those with more than one type of symptom) tended to have lower accuracies and should be avoided in future diagnostic system revisions. None of the four diagnostic systems includes separate criteria that represent all three core domains of delirium (cognitive, circadian, higher order thinking).

In summary, ours is the first evaluation of four classification systems for delirium diagnosis that utilized comparisons of accuracy to an "agnostic" rating of symptoms using the DRS-R98 by an independent rater, and assessed classification performance characteristics of each system. This approach lends itself to discernment of how criteria are written in order to develop an even better set of diagnostic criteria in the future that could truly serve as a reference standard.

6. Study 3:

Subsyndromal Delirium Compared to Delirium, Dementia, and Subjects without Delirium or Dementia in Elderly General Hospital Admissions and Nursing Home Residents

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Submitted to be published.

6.1. Aims

- To describe the phenomenological profile, by the DRS-R98, of the new definition for SSD suggested by Meagher et al. [123] in two geriatric populations from a nursing home and a general hospital.
- To compare the presentation and phenomenology of SSD, FSD (by the DSM-5) and dementia, considering also those subjects without delirium or dementia, in two geriatric settings.
- To evaluate the presence, relevance and relationship of the proposed SSD features by Trzepacz et al. [122] across the groups.

6.2. Hypothesis

- SSD, as defined by the proposed criteria by Meagher et al in 2014, shows an intermediate severity of symptoms between FSD and non-delirium patients, including those with dementia.
- FSD and SSD have a similar phenomenological profile in the two geriatric settings.
- The three core domains of delirium symptoms, and more specifically the five symptoms proposed by Trzepacz et al. (sleep-wake cycle disturbance, thought process abnormalities, orientation, attention and visuospatial ability) are useful to differentiate FSD and SSD from dementia and nondelirium or dementia subjects

6.3. Methods

6.3.1. Subjects

Subjects derive from two prospective cross-sectional studies that used similar methods of assessment for delirium status and phenomenology: (i) a sample of 200 consecutive elderly acute general medical admissions to a university teaching hospital (GH) in Sligo (Ireland) [40], and (ii) a group of 200 consecutive patients admitted to a Skilled Nursing Home (NH) in Reus (Spain)[222].

All patients aged 70 years and older newly admitted to the GH were asked to participate in the study within the first 72 hours after admission. All patients admitted to the NH were assessed during the first 24 to 48 hours. In both samples, patients were excluded if (i) they had been studied on a previous admission, and (ii) they had severe communicative problems or did not speak the respective native language (English or Spanish). Of 439 eligible patients, 39 were excluded. The exclusions reflected a variety of reasons including: lack of consent (n= 15), severe language disorder / aphasia (n= 14), coma/sedation (n =6), severe sensory problem (n= 2), inability to speak Spanish (n =2). In each setting patients were recruited consecutively until 200 subjects were included, allowing for a final sample of 400 subjects.

In the GH sample, assessments were conducted by two trained raters experienced in administering the scales with high inter-rater reliability established prior to the study. Each participant was interviewed by the same rater with the full battery of scales. Patients from the NH sample were evaluated independently by two experienced raters after running a pilot test with 10 patients (not included in the study sample) to evaluate logistic difficulties and possible problems in using research instruments. The first rater evaluated patients using DSM-5 criteria, while the second rater (specifically trained in DRS-R98 administration) administered the Spanish DRS-R98. A third researcher contacted the family or a caregiver to administer the Spanish-IQCODE.

Demographic (including gender, age) and clinical data were collected from files and medical records.

6.3.2. Delirium

We evaluated each patient for delirium using DSM-5 criteria [27] according to all available information from assessment of the patient, discussion with nursing staff and available collateral sources. In the GH sample, to test “awareness” for the A criterion, researchers used the relevant item from the Reversible Cognitive Dysfunction Scale (RCDS) [223,224]. The item has a four -point range however, for this analysis a binary (normal/abnormal) rate was assigned, by collapsing the three categories of abnormality into one. In the NH sample, researchers designed a diagnostic criteria checklist to systematically rate each single item as present or not according to the subjective impression of the assessing clinician. For the

assessment of awareness, this was based upon the ability of the patient to engage appropriately with their environment and the assessment process, using a binary approach (yes/no) where any alteration from normal awareness or attention was scored as positive.

The Delirium Rating Scale-Revised-98 (DRS-R98) [45] is a validated tool used to evaluate the delirium phenomenological profile. This scale includes phenomenological descriptive anchors for 13 severity (rated from 0 to 3) and 3 diagnostic items (rated 0 to 2 or 3) where the DRS-R98 Severity scale has a maximum score of 39 and the DRS-R98 Total scale has 46, with higher scores indicating more severe delirium. Items can be subgrouped to represent symptoms of the 3 core domains of delirium (cognitive, circadian, higher order thinking). The scale has shown very good validity and inter-rater reliability values in all its versions, including the original in English [45] and also the Spanish translation [126,221].

6.3.3. Dementia

In the Irish sample, dementia was defined using DSM-5 criteria (major neurocognitive disorder) according to all available sources (medical files, GP files, collateral history and evidence from neuroimaging reports).

The Spanish - Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) was used for the Spanish sample. This is a structured interview comprising 26 questions made to an informant about the patient's cognition and function during the preceding five years. Scores range from 26 to 130. The validated Spanish version uses a cut-off >85 for possible dementia [217].

6.3.4. Study groups

Patients who met DSM-5 criteria for delirium were classified as FSD. For the SSD group, we used criteria described by Meagher and coworkers [123] whereby patients with SSD were defined as: 1) No diagnosis of DSM-5 delirium, 2) acute or subacute onset of symptoms as defined by a score of ≥1 for item #14 of DRS-R98 (temporal onset of symptoms), 3) Inattention as defined by a score of ≥1 in item #10 of DRS-R98 (attention), and 4) a score ≥1 on at least one other symptom of the DRS-R98 Severity scale.

The dementia-only group (i.e., dementia without SSD or FSD) was obtained from dementia cases as described above.

Subjects who did not meet DSM-5 criteria for delirium or the SSD definition used herein and did not have a previous dementia were classified as No-Delirium No-Dementia (NDND) group.

6.3.5. Ethical approval

The study was approved by the Institutional Review Board and the Research Ethics Committees at each centre. The procedures and rationale for the study were explained to all patients and relatives but because many patients had cognitive impairment at study entry it was presumed that some might not be capable of giving informed written consent. Because of the non-invasive nature of the study, ethics committee approval was given to augment patient assent with proxy consent from next of kin (where possible) or a responsible caregiver for all participants, in accordance with the Helsinki Guidelines for Medical Research involving human subjects [225].

6.3.6. Statistical Analysis

Data were analysed using SPSS v 21 (IBM). Continuous variables are expressed as means ± standard deviation (SD) and discrete variables as frequencies and percentages (%).

Chi-square test was used to compare gender, presence of dementia, and frequencies of the four study groups between GH and NH facilities; and t-test for comparison of age (significance set at $p \leq 0.05$).

To evaluate internal consistence of DRS-R98 in this combined sample, Cronbach's α was performed for its Total and Severity scale items in the whole sample and in both GH and NH samples.

For comparison of the DRS-R98 diverse scores among groups we used Mann-Whitney U test (pairwise comparisons) and Kruskal Wallis ANOVA with post hoc pairwise comparisons with Mann-Whitney U. We used chi-square to compare the frequency of occurrence of scores ≥1 or ≥2 for individual DRS-R98 items. The p-value was set at <0.001 for multiple pairwise comparisons.

6.4. Results

6.4.1. Sample description

The demographic and general clinical characteristics of the patients from each group, and internal consistency for DRS-R98 are shown in **Table 6.1**. The mean age for the whole sample was 79.7 ± 8.5 years, 50.8% were women and 60.8% had pre-existing dementia. The groups differed in mean age (81.1 ± 6.5 for GH and 78.3 ± 9.9 for NH sample, p =0.001), but not for gender or occurrence of dementia. The internal consistency of the merged GH and NH DRS-R98 scores was excellent, with both facilities having very similar consistency and with regard to the merged dataset.

Table 6.1. Clinical and demographic characteristics of the sample
Of 400 patients from a skilled nursing home (NH) and a university teaching general hospital (GH). Values are expressed in mean ± SD for age, number (%) for gender and previous cognitive impairment, and Cronbach's α coefficient for internal consistency of DRS-R98 scores between the cohorts.

Variable	Whole Sample (n= 400)	NH (n=200)	GH (n= 200)
Age*	79.7±8.5	78.3±9.9	81.1±6.5
Gender - male	197 (49.3)	97 (48.5)	100 (50.0)
Previous dementia	243 (60.8)	117 (58.5)	126 (63.0)
DRS-R98 Severity Scale Cronbach's α	0.861	0.891	0.832
DRS-R98 Total Scale Cronbach's α	0.892	0.917	0.861

* NH <GH (p =0.001).

In terms of classification into study groups, 80 patients (20.0%) had FSD, 77 (19.3%) SSD, 119 (29.8%) dementia-only, and 124 (31%) were in the NDND group. FSD frequency was significantly higher in the NH group (27% vs 13%) (p <0.001), while the GH group had a higher frequency of dementia-only (35% versus 24.5%, p =0.02). There were no differences for frequency of SSD or NDND between the two settings.

DRS-R98 Severity and Total scale scores significantly distinguished all four groups, with a pattern of ascending burden of delirium severity by diagnostic group: NDND <dementia-only <SSD <FSD, where DRS-R98 Total scores ranged from 3.4±2.9 to 20.9±7.2.

6.4.2. Comparison of DRS-R98 mean item scores by group

Table 6.2 shows DRS-R98 mean item scores according to the various neurocognitive disorders. Notably, noncore symptoms (items #2, #3 and #4) frequently did not discriminate among groups, whereas core items did.

Greater mean severity of core symptoms distinguished both delirium groups from NDND and dementia-only groups. Specifically, these were orientation, attention, and visuospatial ability (cognition), language and thought process abnormalities (higher level thinking), and sleep-wake cycle, motor agitation and retardation (circadian) items.

Short term and long term memory scores were less impaired in the NDND group than all other groups, while long term memory was less impaired in dementia-only compared with both delirium groups.

SSD was distinguished from NDND group by all items. But SSD was only distinguished from FSD by less severe impairment of orientation, attention and

visuospatial ability. Notably, SSD was not distinguished from FSD by scores on temporal onset or physical attribution.

Table 6.2. DRS-R98 scores for 400 elderly subjects by diagnostic group.
Full syndromal delirium (FSD), subsyndromal delirium (SSD), dementia-only, and no-delirium no-dementia (NDND). Scores are expressed as means ± SD and compared between groups with Kruskal Wallis ANOVA (post hoc pairwise comparisons with Mann-Whitney U). Footnotes describe details of score comparisons. All p values for multiple pairwise comparisons were set at <0.001.

DRS-R98	NDND (n=124)	Dementia (n=119)	SSD (n=77)	FSD (n=80)
1. Sleep-wake cycle disturbance[~°†¶$]	0.53±0.62	0.67±0.75	1.17±0.77	1.50±0.76
2. Perceptions and hallucinations[~°†]	0.07±0.41	0.24±0.76	0.64±1.11	0.41±0.87
3. Delusions[~°]	0.09±0.44	0.24±0.76	0.42±0.85	0.28±0.71
4. Lability of affect[~°†¶]	0.04±0.20	0.18±0.43	0.40±0.61	0.53±0.66
5. Language[~°†¶$]	0.06±0.33	0.18±0.49	0.68±0.82	1.20±1.07
6. Thought process abnormalities[~°†¶$]	0.10±0.30	0.19±0.47	0.71±0.76	1.28±1.04
7. Motor agitation[~°†¶$]	0.05±0.22	0.11±0.34	0.61±0.73	0.81±0.90
8. Motor retardation[~°†¶$]	0.12±0.35	0.13±0.34	0.73±0.81	1.16±0.96
9. Orientation[~°†¶$‡§]	0.17±0.45	0.69±0.84	1.27±0.81	2.04±0.82
10. Attention[~°†¶$‡]	0.15±0.38	0.26±0.50	1.42±0.57	1.89±0.78
11. Short-term memory[~°†§]	0.43±0.78	1.06±1.14	1.30±1.19	1.50±1.19
12. Long-term memory[~°†¶$§]	1.01±1.02	1.60±1.09	2.21±0.99	2.49±0.86
13. Visuospatial ability[~°†¶$‡§]	0.31±1.08	0.71±0.86	1.42±0.85	1.96±0.91
14. Temporal onset of symptoms[~°†¶$]	0.06±0.26	0.22±0.52	1.49±0.66	1.65±0.81
15. Fluctuation of symptom severity[~°†¶$]	0.00±0.00	0.03±0.18	0.44±0.57	0.75±0.63
16. Physical disorder[~°†¶$]	0.27±0.62	0.43±0.78	1.14±0.88	1.45±0.74
DRS-R98 Severity[~°†¶$‡§]	3.11±2.64	6.26±3.68	12.96±5.41	17.10±6.35
DRS-R98 Total[~°†¶$‡§]	3.44±2.90	6.94±4.13	16.01±6.18	20.89±7.25

~° NDND <SSD.
† NDND <FSD.
¶ Dementia <FSD.
$ Dementia <SSD.
‡ SSD <FSD.
§ NDND <dementia.

Dementia-only was distinguished from delirium groups by its lower scores in all items except for perception, delusions, lability of affect, and short-term memory. Dementia-only differed from NDND by its higher score in almost all cognitive items, except attention.

6.4.3. Comparison of DRS-R98 item score frequencies by group

Item frequencies also distinguished some groups (**Supplemental Tables 1 and 2**). Item scores ≥1 on all DRS-R98 items differentiated SSD from NDND.

NDND had significantly fewer patients with score ≥1 than dementia-only for orientation, short term memory, and visuospatial ability items.

Supplemental Table 6.1. Frequencies of DRS-R98 scores ≥ 1
For 400 elderly subjects by diagnostic group: full syndromal delirium (FSD), subsyndromal delirium (SSD), dementia-only, and no-delirium no-dementia (NDND). Frequencies are expressed as percentages and compared between groups with Chi-square, p values at <0.001 (Footnotes describe details of score comparisons).

DRS-R98	NDND (n=124)	Dementia (n=119)	SSD (n=77)	FSD (n=80)
1. Sleep-wake cycle disturbances[~°†¶$]	46.8	52.1	81.8	88.8
2. Perceptions and hallucinations[~°†]	4.0	10.1	28.6	23.8
3. Delusions[~°]	4.8	10.9	24.7	16.3
4. Lability of affect[~°†¶]	4.0	16.8	35.1	45.0
5. Language[~°†¶$]	4.8	15.1	48.1	67.5
6. Thought process abnormalities[~°†¶$]	9.7	16.8	54.5	72.5
7. Motor agitation[~°†¶$]	4.8	10.1	46.8	52.5
8. Motor retardation[~°†¶$]	11.3	13.4	51.9	70.0
9. Orientation[~°†¶$§]	13.7	47.9	83.1	95.0
10. Attention[~°†¶$]	13.7	23.5	100	96.3
11. Short-term memory[~°†§]	29.0	54.6	62.3	70.0
12. Long-term memory[~°†]	61.3	79.0	90.9	96.3
13. Visuospatial ability[~°†¶$§]	20.2	47.9	85.7	95.0
14. Temporal onset of symptoms[~°†¶$]	4.8	17.6	100	95.0
15. Fluctuation of symptom severity[~°†¶$]	0.8	3.4	40.3	65.0
16. Physical disorder[~°†¶$]	18.5	25.2	67.5	85.0

~° NDND <SSD
† NDND <FSD
¶ Dementia <FSD
$ Dementia <SSD
§ NDND <dementia
Note: SSD v. FSD: no differences.

When compared with the dementia-only group, both delirium groups had a higher frequency of scores ≥1 for all items evaluating core delirium domains, except for both memory items, and psychotic symptoms (items #2, #3).

Moreover, frequencies for core domain items with scores ≥2 were significantly higher in FSD compared to NDND and dementia-only, but significantly higher only for orientation and attention when compared to SSD. Frequency of item scores ≥2 on language, thought process, motor retardation, motor agitation, attention and visuospatial ability items were significantly higher in SSD than dementia-only.

Supplemental Table 6.2. Frequencies of DRS-R98 scores ≥ 2
For 400 elderly subjects by diagnostic group: full syndromal delirium (FSD), subsyndromal delirium (SSD), dementia-only, and no-delirium no-dementia (NDND). Frequencies are expressed as percentages and compared between groups with Chi-square, p values at <0.001 (Footnotes describe details of score comparisons).

DRS-R98	NDND (n=124)	Dementia (n=119)	SSD (n=77)	FSD (n=80)
1. Sleep-wake cycle disturbances[~]†¶	6.5	13.4	31.2	56.3
2. Perceptions and hallucinations[~]	1.6	7.6	20.8	10.0
3. Delusions	2.4	7.6	10.4	7.5
4. Lability of affect	0	1.7	3.9	6.3
5. Language[~]†¶$	0.8	2.5	16.9	36.3
6. Thought process abnormalities[~]†¶$	0	1.7	15.6	38.8
7. Motor agitation[~]†¶$	0	0.8	14.3	25.0
8. Motor retardation[~]†¶$	0.8	0	19.5	37.5
9. Orientation[~]†¶‡§	3.2	17.6	39.0	78.8
10. Attention[~]†¶‡$	0.8	2.5	37.7	71.3
11. Short-term memory[~]†¶§	9.7	35.3	45.5	52.5
12. Long-term memory[~]†¶§	27.4	54.6	77.9	83.8
13. Visuospatial ability[~]†¶$§	3.2	20.2	46.8	67.5
14. Temporal onset of symptoms[~]†¶$	0.8	3.4	40.3	53.8
15. Fluctuation of symptom severity†	0	0	3.9	10.0
16. Physical disorder[~]†¶$	8.9	17.6	46.8	60.0

[~] NDND <SSD.
† NDND <FSD.
¶ Dementia <FSD
$ Dementia <SSD.
‡ SSD <FSD.
§ NDND <dementia.

6.4.4. Comparison of delirium phenomenology by clinical setting

Comparison of DRS-R98 item scores between the Spanish NH and Irish GH samples revealed few differences (**Table 6.3**). Short-term memory was worse in GH for all groups, whereas thought process abnormalities were worse in NH for the NDND, dementia and SSD groups. Also, in only the dementia group, sleep-wake cycle was more impaired in GH whereas orientation was more impaired in NH. Fluctuation was more severe in NH vs. GH for the FSD group.

Table 6.3. DRS-R98 scores for the 400 subjects according to clinical setting.
For each of the 4 diagnostic groups (NDND, Dementia-only, SSD, FSD). Values are expressed in means ± SD; p values between sites within each group. Pairwise comparisons are made by the Mann-Whitney U.

DRS-R98	NDND (n=124)		Dementia-only (n=119)		SSD (n=77)		FSD (n=80)	
	NH (n=63)	GH (n=61)	NH (n=49)	GH (n=70)	NH (n=34)	GH (n=43)	NH (n=54)	GH (n=26)
1. Sleep-wake cycle disturbance	0.43±0.53	0.64±0.68	0.37±0.49	0.89±0.83*	0.97±0.67	1.33±0.81	1.61±0.71	1.27±0.83
2. Perceptions and hallucinations	0.13±0.55	0.02±0.13	0.33±0.90	0.17±0.64	0.71±1.12	0.58±1.12	0.50±0.93	0.23±0.71
3. Delusions	0.17±0.61	0	0.51±1.04	0.06±0.38	0.71±1.03	0.19±0.59	0.35±0.83	0.12±0.33
4. Lability of affect	0.06±0.25	0.02±0.13	0.27±0.53	0.13±0.34	0.59±0.66	0.26±0.54	0.56±0.69	0.46±0.58
5. Language	0.10±0.43	0.03±0.18	0.33±0.66	0.09±0.28	0.79±0.91	0.58±0.73	1.41±1.02	0.77±1.07
6. Thought process abnormalities	0.19±0.40	0*	0.39±0.64	0.06±0.23*	1.06±0.73	0.44±0.67*	1.43±1.02	0.96±1.04
7. Motor agitation	0.03±0.18	0.07±0.25	0.08±0.34	0.13±0.34	0.68±0.81	0.56±0.67	0.89±0.90	0.65±0.89
8. Motor retardation	0.11±0.32	0.13±0.39	0.16±0.37	0.11±0.32	0.76±0.89	0.70±0.74	1.39±0.98	0.69±0.74
9. Orientation	0.25±0.57	0.08±0.28	1.10±0.85	0.40±0.71*	1.50±0.83	1.09±0.75	2.07±0.84	1.96±0.77
10. Attention	0.19±0.43	0.10±0.30	0.31±0.55	0.23±0.46	1.29±0.52	1.51±0.59	1.91±0.85	1.85±0.61
11. Short-term memory	0.06±0.30	0.80±0.93*	0.37±0.83	1.54±1.07*	0.62±1.04	1.84±1.02*	1.04±1.10	2.46±0.71*
12. Long-term memory	0.89±1.03	1.13±0.99	1.78±0.98	1.47±1.15	2.24±1.05	2.19±0.96	2.33±0.97	2.81±0.40
13. Visuospatial ability	0.11±0.32	0.51±1.48	0.57±0.91	0.81±0.82	1.24±0.99	1.56±0.70	2.06±1.00	1.77±0.65
14. Temporal onset of symptoms	0.03±0.18	0.08±0.33	0.18±0.39	0.24±0.60	1.41±0.56	1.56±0.73	1.76±0.80	1.42±0.81
15. Fluctuation of symptoms	0	0	0	0.06±0.23	0.62±0.60	0.30±0.51	0.94±0.56	0.35±0.56*
16. Physical disorder	0.13±0.38	0.43±0.76	0.22±0.47	0.57±0.91	1.38±0.70	0.95±0.97	1.61±0.56	1.12±0.95
Severity Scale	2.73±2.52	3.52±2.72	6.55±3.72	6.09±3.68	13.21±6.15	12.81±4.90	17.63±7.05	16.00±4.48
Total Scale	2.89±2.71	4.03±3.00	6.96±3.82	6.96±4.36	16.56±6.62	15.63±5.92	21.85±7.82	18.88±5.51

* Values with significant difference ($p < 0.001$) between the two sites.

6.4.5. The impact of dementia on DRS-R98 profiles for SSD and FSD

Table 6.4 shows a comparison of SSD and FSD subgroups with and without comorbid dementia, where 63/77 SSD (82%) and 61/80 FSD (76%) had comorbid dementia. For both SSD and FSD, mean DRS-R98 Severity and Total scores were at least 3 points higher (worse) in the comorbid subgroup, but there was no statistically significant difference on mean scores between subgroups with or without dementia.

Table 6.4. Comparison of DRS-R98 scores for elderly patients with SSD and FSD.
Between subgroups with or without comorbid dementia. Values are in means ± SD. Pairwise comparisons made using Mann-Whitney U found no differences at $p < 0.001$ for any item between subgroups by dementia status.

DRS-R98	SSD Without Dementia (n=14)	SSD With Dementia (n=63)	FSD Without Dementia (n=19)	FSD With Dementia (n=61)
1. Sleep-wake cycle disturbance	0.93±0.92	1.22±0.73	1.47±0.77	1.51±0.77
2. Perceptions and hallucinations	0.43±0.94	0.68±1.15	0.16±0.37	0.49±0.96
3. Delusions	0.00±0.00	0.51±0.91	0.11±0.46	0.33±0.77
4. Lability of affect	0.21±0.43	0.44±0.64	0.42±0.61	0.56±0.67
5. Language	0.50±0.65	0.71±0.85	1.16±0.90	1.21±1.13
6. Thought process abnormalities	0.43±0.65	0.78±0.77	1.11±0.88	1.33±1.09
7. Motor agitation	0.36±0.50	0.67±0.76	0.58±0.96	0.89±0.88
8. Motor retardation	0.57±0.85	0.76±0.80	1.16±0.96	1.16±0.97
9. Orientation	1.00±0.68	1.33±0.82	1.74±0.93	2.13±0.76
10. Attention	1.43±0.65	1.41±0.56	1.63±0.90	1.97±0.73
11. Short-term memory	0.93±1.07	1.38±1.21	0.79±1.03	1.72±1.16
12. Long-term memory	1.86±1.23	2.29±0.92	1.95±0.97	2.66±0.75
13. Visuospatial ability	1.43±0.85	1.41±0.85	1.68±0.75	2.05±0.94
14. Temporal onset of symptoms	1.43±0.65	1.51±0.67	2.00±0.82	1.54±0.79
15. Fluctuation of symptom severity	0.14±0.36	0.51±0.59	0.79±0.71	0.74±0.60
16. Physical disorder	1.00±0.96	1.17±0.87	1.63±0.68	1.39±0.76
Severity Scale	10.07±3.91	13.63±5.56	14.05±5.94	18.05±6.22
Total Scale	12.64±4.20	16.79±6.37	18.37±7.11	21.67±7.17

Table 6.5 compares the phenomenological profile of subjects with dementia according to their delirium syndromal status (dementia-only, dementia with SSD, dementia with FSD). For the DRS-R98 Severity and Total scales there was a significant ($p<0.001$) gradient of increasing scores across groups from dementia-only to dementia with SSD to dementia with FSD.

Table 6.5. DRS-R98 scores for the 243 patients with dementia.
According to diagnostic groups: full syndromal delirium (FSD), subsyndromal delirium (SSD) and dementia-only. Values expressed as means ± SD. Comparisons made by Kruskal Wallis ANOVA, with Mann-Whitney U post hoc pairwise analysis. Significance at $p <0.001$.

DRS-R98	Dementia without delirium (n=119)	Dementia with SSD (n=63)	Dementia with FSD (n=61)
1. Sleep-wake cycle disturbance*†	0.67±0.75	1.22±0.73	1.51±0.77
2. Perceptions and hallucinations	0.24±0.76	0.68±1.15	0.49±0.96
3. Delusions	0.24±0.76	0.51±0.91	0.33±0.77
4. Lability of affect†	0.18±0.43	0.44±0.64	0.56±0.67
5. Language*†	0.18±0.49	0.71±0.85	1.21±1.13
6. Thought process abnormalities*†	0.19±0.47	0.78±0.77	1.33±1.09
7. Motor agitation*†	0.11±0.34	0.67±0.76	0.89±0.88
8. Motor retardation*†	0.13±0.34	0.76±0.80	1.16±0.97
9. Orientation*†$	0.69±0.84	1.33±0.82	2.13±0.76
10. Attention*†$	0.26±0.49	1.41±0.56	1.97±0.73
11. Short-term memory†	1.06±1.14	1.38±1.21	1.72±1.16
12. Long-term memory*†	1.60±1.09	2.29±0.92	2.66±0.75
13. Visuospatial ability*†$	0.71±0.86	1.41±0.85	2.05±0.94
14. Temporal onset of symptoms*†	0.22±0.52	1.51±0.67	1.54±0.79
15. Fluctuation of symptom severity*†	0.03±0.18	0.51±0.59	0.74±0.60
16. Physical disorder*†	0.43±0.78	1.17±0.87	1.39±0.76
Severity Scale*†$	6.28±3.69	13.63±5.56	18.05±6.22
Total Scale*†$	6.96±4.13	16.79±6.37	21.67±7.17

* Dementia-only <SSD.
† Dementia-only <FSD.
$ SSD <FSD.

Additionally, the majority of DRS-R98 items had a similar pattern when contrasting dementia-only to the delirium/dementia comorbid groups, though not significantly for all items. SSD with dementia was significantly higher than dementia-only on all items except for short-term memory, delusions, perceptual disturbances and lability of affect. FSD with dementia was significantly higher than dementia-only on all items except for delusions and perceptual disturbances. However, FSD with dementia was significantly higher than SSD with dementia only on orientation, attention, and visuospatial ability.

6.5. Discussion

We describe the delirium phenomenological profiles of elderly patients from general hospital and nursing home settings in two countries with focus upon the role of comorbid dementia and the challenges of detecting SSD in older persons. We pooled data for our group analyses of DRS-R98 data for delirium profile descriptions. To define the SSD group, we applied the recently proposed Meagher et al clinical criteria [123]. We found that SSD differed from dementia-only and NDND groups on severity of most DRS-R98 items, but from FSD only for severity of symptoms representing one of the three core domains of delirium: cognitive (as evidenced by impaired attention, orientation, and visuospatial function) but not higher level thinking or circadian functions. Overall, these results from two different clinical settings in elderly patients with high rates of comorbid dementia replicate findings from previous work comparing FSD and SSD but using different definitions of SSD [48,49,51,105,122]. Additionally, we found that dementia comorbidity did not significantly affect delirium severity within SSD or FSD groups such that delirium overshadows dementia symptoms, in keeping with the majority of previous studies [35,59,146,182,185,189,195,198–200].

We also found support for the more explicit SSD symptom description as proposed by Trzepacz et al [122] whereas the Meagher et al criteria [123] do not specify the required number or type of symptoms besides inattention ("evidence of other cognitive and/or neuropsychiatric disturbances") and allow for scores to be greater than mild severity. In contrast, DRS-R98 items representing all three core domains (#1, 6, 9, 10 and 13) are required to be present at mild severity by the Trzepacz et al criteria. Though those were present in the majority of our SSD group that had been diagnosed using the Meagher et al [123] criteria, these "looser" criteria did not distinguish as many core domain items in SSD vs FSD perhaps because of fewer requirements or sample differences. Nonetheless, frequencies of scores ≥1 for items representing Trzepacz et al criteria in SSD group ranged from 81.8% for sleep-wake cycle disturbance to 100% for attention, with the exception that mild thought process abnormalities were present in only 54.5%. A higher proportion of FSD than SSD cases were rated as moderately affected (2 points) on attention and orientation. Both systems signal that an acute change in mental status with even a mild impairment of that symptom cluster should suggest SSD to a clinician.

The phenomenological profile of DSM-5 FSD delirium and SSD defined by the criteria used herein [123] was very similar across the two clinical populations with some minor differences. Short-term memory impairment was higher in GH both for SSD and FSD, thought process abnormality higher in NH for SSD and fluctuation higher in NH for FSD, probably reflecting underlying characteristics of the populations (e.g. thought process item was also higher in NH and short-term memory in GH for NDND and dementia-only groups).

Interestingly, the NH sample had more FSD cases than the GH (27% vs. 13%), although the total for delirium spectrum disorders (FSD or SSD) was comparable across the populations. This study reports the first comparison between two settings using DSM-5 criteria, but previous work has suggested that the

inclusiveness of diagnostic systems can vary according to the setting where they are applied [33,140]. Alternatively, sampling/recruitment approaches may have affected the results. Also, the frequency of delirium in post-acute care services varies widely across reports, ranging from 6% to 33.3% [152,153,168,226], with higher rates identified in populations with more severe dementia and physical comorbidity [153]. The NH described herein caters for a complex group of patients with a high prevalence of severe cognitive disorders and medical-surgical problems, which may account for the high frequency of delirium in that sample. The frequency of FSD in the GH group was lower than that reported in some studies involving similar populations [140] but when combined with the SSD group comprised more than one third of patients from the GH grouping, which is congruent with previous work [123]. Of note, the frequency of SSD was similar between the two sites (17% vs. 21.5%), highlighting the consistency of this phenomenon across clinical settings.

The severity of delirium symptoms in the SSD group was intermediate between FSD and the non-delirium groups (NDND and dementia-only), which differed mainly in terms of the severity of three-core domain symptoms [48] as previously reported in studies that have defined SSD in different ways to this work [105,122,123]. Trzepacz et al [122] applied binary logistic regression to find that DRS-R98 item scores for six core domain symptoms (sleep-wake cycle, thought process, language, attention, orientation, and visuospatial ability) when taken together at mild severity (item score of 1 point), correctly classified 80% of SSD vs no delirium.

Previous studies indicate that delirium overshadows symptoms of dementia when they are comorbid [35,55,59,146,182,185,189,195,198–200] and the three core domains are specifically affected in delirium subjects, with or without comorbid dementia, in a way that makes them different from non-delirious patients, including those with only dementia [59]. Though our sample size of nondemented SSD patients was relatively small, our findings support others' that delirium overshadows dementia symptoms when comorbid.

The five items proposed by Trzepacz et al. [122] distinguished SSD comorbid with dementia from dementia alone and moreover, three of these items (attention, orientation and visuospatial ability) differentiate also SSD from FSD, which suggests focusing on those three symptoms may be useful when detecting delirium, even among those with dementia. This gradient of increasing scores across dementia-only to the delirium/dementia comorbid groups, highlights the cumulative neuropsychiatric burden attributable to delirium.

Our study has a number of limitations. First, evaluations were conducted in two different countries, by different researchers and using different language versions of the DRS-R98. However, the DRS-R98 has high inter-rater reliability established in all its validation studies, researchers at both settings were highly expert in delirium assessment, and experienced and specifically trained in the use of the DRS-R98. Further, internal consistency of DRS-R98 items was excellent and similar across these two samples. Also, the DSM-5 criteria are only recently published and discrepancies may exist in the way some criteria are interpreted by different raters

[39,40,227]. The approach to establishing unawareness as well as the presence of previous cognitive impairment or dementia differed at the two sites (i.e., clinical criteria vs Spanish-IQCODE for dementia), which could explain some of the differences in the populations' characteristics. Finally, we did not consider the possible impact of other neuropsychiatric conditions (e.g. depression) that are common in elderly patients. However, uniquely, we addressed the impact of dementia on SSD phenomenology.

And we ascertained that when using the Meagher et al [123] proposed SSD criteria to define the SSD group, we largely supported prior literature on its severity being distinguishable from FSD and nondemented-nondelirious controls. SSD, when using these criteria, found symptom severity from the cognitive core domain as distinguishing FSD from SSD, though it might be possible that if these criteria were more explicit and required symptoms and severity representing all three core domains, the results may have been significantly different for severity of the other core domain symptoms as well. More research is needed for applying explicit SSD criteria requiring all core domain symptoms. Nonetheless, this work still adds more specificity to the understanding of SSD than previous work using total scale score ranges.

In conclusion, we found that both FSD and SSD are common in elderly patients receiving care in acute general hospital and nursing home settings, with those populations having a similar phenomenological profile for DSM-5 defined delirium. Also, for both populations, SSD has a phenomenological intensity that is intermediate between non-delirium and FSD, independent of the presence of comorbid dementia.

7. GENERAL DISCUSSION

In this work we analysed the delirium concept under different diagnostic systems: the definition from three editions of the DSM (III-R, IV and 5)[19,20,27] and ICD-10 [23] and the new proposal for Subsyndromal Delirium [123]. We used the DRS-R98 scale [45] for analysis where, after evaluating its performance against the different delirium classifications, it was the base for creating "agnostic" groups of delirium patients, which were used as a standard for criteria comparison and as a reliable method to measure the severity of the delirium symptoms.

7.1.The delirium diagnostic criteria

DSM evolution has been projected to improve its reliability and, with this purpose, criteria have undergone a successive simplification, giving special emphasis to cognition but leaving aside other core symptoms, particularly circadian and higher level thinking [21,32]. The results of our work show how this evolution has lead to an effective increase in reliability levels, where DSM-5 had the best inter-rater reliability and DSM-III-R the worst -only better than ICD-10, as previously described [33,43]. However, it is worth noting that values for all DSMs fell in the good range (kappa from 0.62 to 0.73).

Solution to reliability problems through simplification and elimination of symptoms has led, however, to a reduction in accuracy. This was confirmed by finding the best accuracy values using DSM-III-R criteria followed by DSM-IV, ICD-10 and DSM-5, in a trend mirroring (in reverse) DSM changes. The "problematic" item of disorganized thinking, only evaluated in the DSM-III-R due to the probable difficulty of its assessment [25], effectively obtained the worst reliability value but, on the other hand, obtained good sensitivity (89.8%), specificity (79.5%) and total accuracy values (82.0) in individual evaluations, reflecting its importance in delirium diagnosis. Hence, probable deficiencies should be sought with the manner this and other complex items are stated on criteria, making communication between clinicians more difficult.

We also showed how DSM-III-R criteria were the most inclusive, even over the simpler DSM-5, as already suggested in previous works [25,33,36–38]. The limited overlap between delirium diagnostic systems shows some patients only covered by one of them (specially the DSM-III-R), whereas ICD-10 patients are enclosed in any other. ICD-10 subjects had more severe symptoms, leaving those with intermediate severity out, including subjects probably affected of SSD.

Although the wider definition of FSD by the DSM-5 produced some overlap on DRS-R98 scores with SSD, the latter category captured also subjects diagnosed as no- delirium, so that even the most inclusive delirium criteria leaves patients with delirium symptoms without clinical recognition, of prognostic relevance regardless of the SSD definition used [67,115,117,123,152,174,176,203,204,206,208,210].

This makes evident the necessity to include SSD in future classifications. Also, SSD was phenomenologically distinguishable from dementia and subjects without SSD/FSD or dementia, even when the latter scored in some delirium symptoms.

It has been already described that neurocognitive alterations could be common to the general and, specially, geriatric populations [151], highlighting the need for robust and reliable tools for delirium study, particularly in older and demented people.

Future criteria must be built around the three core domains of symptoms (cognitive, circadian and higher level thinking), which clearly differentiate delirium (in its full syndromal or subsyndromal status) from non-delirium, even when other neurocognitive disorders coexist, as we further demonstrated in this work [47–57,122,194]. Also, any new classification has to use simple criteria, anchored in clear descriptions for each criterion in order to ensure high reliability and besides this, it is important to continue the search for a consistent biomarker, which would allow us to obtain a more accurate delirium standard.

7.2. The DRS-R98 scale

The DRS-R-98 has proven to be a very valuable tool for the study of delirium in a variety of ways. It is useful for the assessment of delirium symptoms, with a clear identification of the core delirium symptoms independently of the diagnostic criteria being used to obtain the diagnosis and giving also a very stable cut-off value for our particular population, in which dementia is an important issue. It was able to differentiate correctly patients without delirium or dementia and those with only dementia from SSD and FSD subjects, in a gradient concordant with the expected severity of symptoms in each diagnostic group. Again, the three core domains of symptoms were especially relevant. When two populations of geriatric patients from different units (acute hospitalisation and nursing home) were compared, the scale performed very well independently of the setting, but also helped to determine differences on the severity of symptoms specifically associated to the clinical context, as previously described [31,134].

Populations with high prevalence of dementia are specially challenging in the diagnosis of delirium [71,191–193]. Consequently, all diagnostic criteria (and particularly ICD-10) showed a reduction in total accuracy, specificity and sensitivity when performed in a demented sample with the DRS-R98 as reference standard. In the same sense, when the DRS-R-98 performed against the diagnosis of delirium made using each diagnostic criteria system, it had a significant worst performance in the demented sample. The scale worked best, in both the total and the demented sample, with the DSM-III-R -and worst by the ICD-10. Despite these differences, the scale obtained very stable cut-off values independently of the diagnosis criteria or the dementia status of the sample. All these make the DRS-R98 a very useful tool for the study of delirium in demented people.

The DRS-R98 is an important tool in the phenomenological study of delirium, and it of proven utility in a variety of settings and diagnostic groups [45,126–133]. We added our specific populations and demonstrated its ability to evaluate the phenomenology of the syndrome, independently of the categories used to define it.

7.3. Searching for a delirium "gold standard"

The natural grouping of symptoms evaluated in an "agnostic" way through the DRS-R98, is probably a good approach to study the nosology of the syndrome and could inform the creation of a clinical "gold standard" for delirium diagnosis.

Besides clinical criteria, delirium diagnosis would also benefit from more objective measures as biomarkers. As delirium pathophysiology is not well understood, it has been difficult to determine reliable biological correlates. Research in this field is only dawning and has provided no conclusive results until now. Still, there are many possible mechanisms associated with the pathogenesis of delirium and therefore underlying serum and cerebrospinal fluid biomarkers. These relate for example with cholinergic theory (as the serum anticholinergic activity -SAA-), dopamine alteration (as polymorphisms in the solute carrier family 6, member 3 -*SLC6A3*- gene and in the D2 subtype of dopamine receptor -*DRD2*- gene), the inflammatory path (as the C-reactive protein, the tumour necrosis factor-alpha, interleukin -IL-1beta, IL-6, IL-8, IL-18, anti- inflammatory IL-1 receptor antagonist, monocyte chemotactic protein 1, procalcitonin, human leukocyte antigen-DR, neuronal injury marker, and the cluster of differentiation 68 -CD68-, among others), markers of neuronal injury (the S100 calcium-binding protein B -S100B-, neuron-specific enolase and brain-derived neurotrophic factor –BDNF-, insulin growth factor-1 -IGF-1-, and the Apolipoprotein E –ApoE- ε4 allele), markers associated with a hypothalamic-pituitary- adrenal axis imbalance (cortisol levels or the glucocorticoid receptor gene *NR3C1* -nuclear receptor family 3, group C, member 1- haplotype 4) and even the level of some amino acids (tryptophan or tyrosine, maybe associated with the deregulation of norepinephrine, dopamine, serotonin and melatonin). However, all these possible markers remain controversial [228–233].

Another possible biomarker in delirium is neuroimaging, but, again, results are not conclusive. Computed tomography (CT), magnetic resonance imaging (MRI) or single photon emission computed tomography (SPECT) have showed some patterns for specific causes of delirium [234], and some particular MRI technics showed that ICU patients with longer duration of delirium had specific white matter alterations, smaller brain volumes and worse cognitive function at 3 and 12 months [235,236]. Activity patterns in functional MRI (fMRI) at rest, some of them reversible, were found to be linked to delirium [237], however there were no differences in fMRI during a cognitive task between delirium and no-delirium subjects [238]. We would conclude that none of the current findings allow us to generalise a specific and easily reproducible neuroimaging model for delirium [239].

Since the 1940s, with the earliest works of Engel and Romano [8–10], when a correlation was found between slowing electroencephalogram (EEG) and a reduction in the level of consciousness, both of which potentially reversible when their cause was also reversible, other works have confirmed and broadened those findings. Thus, in patients with hepatic encephalopathy after a morphine or diet injury [240], some differentiating features were found between delirious patients with intra and extra-cranial underlying cause using quantitative EEG techniques [241]; also ICU patients [242] or elder subjects admitted to a general hospital [243]. These findings have also been backed by animal models using atropine [244–246]. Additionally, a relationship has been described between EEG slowing and the severity of cognitive alteration [243,247], delirium severity [243] and length of delirium and hospital stay [247]. In the field of neuropsychiatric comorbidity, patients with Alzheimer disease or multi-infarct dementia have shown a more important alteration on the EEG when suffering also delirium in comparison with those without dementia [247] and some patterns such as the theta activity, relative power in the delta frequency and general slowing in quantitative EEG can be useful to differentiate delirium from dementia without delirium [248,249]. Both conventional and quantitative EEG techniques show specific characteristics to differentiate delirium from normal aging, dementia or other neuropsychiatric conditions. However, quantiative EEG techniques shoud be preferred given their better accuracy, lesser time involved, ease of comparison and use of sophisticated techniques such as neural network models [249,250].

Combinations of clinical and EEG evaluation have been reported to classify correctly a high number of delirious subjects. For example the alteration in the MMSE along with the relative power of alpha in the EEG can correctly identify the 94% of subjects with delirium by the DSM-III-R [248] and an EEG dominant posterior rhythm together with serum albumin and the Trail Making Test B alterations obtained an accuracy of more than 95% for delirious patients with cirrhosis [95]. All these results are indicators that EEG could become a feasible tool for delirium evaluation and could allow a more objective and homogenous characterisation of the syndrome in the future.

Future research has to be implemented to find out which of those possible biomarkers is reliable and easy to apply in daily practice. Only with the combination of this biomarker and phenomenomenologically-based clinical criteria will we dispose of a more objective delirium definition. This way we will arrive to a better understanding of delirium epidemiology, clinical presentation, prevention, treatment and outcomes.

8. General Conclusions

Delirium diagnostic criteria, in this case DSM-5, ICD-10, DSM-IV and DSM-III-R, cover a different extent of delirium symptoms and therefore are tailored to specific groups of patients with little overlap between them.

Validity and reliability values of the DSM editions have been inversely related through their time evolution. ICD-10 obtained poorer results in both measures, with a bigger drop in the demented sample.

SSD, specifically under our definition, is a valid and relevant concept with intermediate severity of symptoms between FSD and subjects without delirium symptoms, including those with dementia.

Performance and reliability of classifications are poorer in patients with dementia, as a known confounding entity.

Future delirium classifications must be based on the three core domains of symptoms (cognitive, circadian and higher level thinking) and contain a specific definition in these terms for SSD.

The DRS-R98 is a valid and useful tool for evaluation of delirium symptoms in geriatric populations from a Spanish skilled nursing home and an Irish general hospital, with very stable cut-off values in the former, independently of the diagnostic criteria used.

The DRS-R98 can correctly classify subjects with and without delirium even without the use of any of the known classification systems and must be a pattern for the creation of a real gold standard for the delirium study.

A gold standard for delirium must be based, beside reliable clinical criteria, on an also reliable biomarker. Current research points out to neuroimaging or, specially, EEG are good candidates.

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PHENOMENOLOGY AND DIAGNOSTIC CRITERIA FOR DELIRIUM AND SUBSYNDROMAL DELIRIUM IN A POPULATION WITH HIGH PREVALENCE OF DEMENTIA. AN EMPIRICAL STUDY.
Esteban Sepúlveda Ramos

9. References

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