Universidade do Minho
Escola de Medicina

José António Briote Mariz

Screening and Diagnosis of Delirium in The Emergency Department - a Case Study in Hospital de Braga

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Screening and Diagnosis of Delirium in The Emergency Department - a Case Study in Hospital de Braga

Tese de Doutoramento
Doutoramento em Medicina

Trabalho realizado sob orientação da
Doutora Nadine Correia Santos, PhD

agosto de 2023

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Rastreio e Diagnóstico de Delirium no Serviço de Urgência (SU) - um Estudo de Caso no Hospital de Braga

RESUMO

O delirium é uma síndrome neuropsiquiátrica frequente, presumivelmente causada por uma desregulação da atividade neuronal basal secundária a distúrbios sistêmicos. No contexto hospitalar, em particular no Serviço de Urgência (SU), o delirium é fator de risco para complicações clínicas, maior tempo de internamento e institucionalização em unidades de cuidados pós-agudos. Em relação aos resultados a longo prazo, os episódios de delirium estão associados a piores resultados de forma independente, mesmo controlando para a idade, sexo, comorbilidades, gravidade da doença e demência de base. No entanto, o delirium continua a ser um grande problema não reconhecido no SU. O primeiro passo no manejo do delirium, em qualquer ambiente hospitalar, é realizar um diagnóstico precoce e preciso, de preferência por meio do uso de um instrumento breve (validado) segundo o algoritmo do Confusion Assessment Method. A avaliação do delirium pode, no entanto, ser dificultada no SU devido às características intrínsecas do seu ambiente. Na presente tese pretendemos, em primeiro lugar, enquadrar o delirium em termos de contexto histórico e fisiopatologia, numa abordagem do estado da arte, com enfase nos cuidados de medicina de urgência. Em seguida, explorámos os indicadores de risco e evolução clínica do delirium na Unidade de Cuidados Intermédios do Serviço de Urgência (UCISU) do Hospital de Braga, num estudo prospectivo e observacional. De relevar, o delirium foi associado a maior tempo de internamento e desfecho desfavorável 1 mês após a alta. Em seguida, foi realizada uma revisão da literatura sobre o conhecimento atual sobre as ferramentas de triagem de delirium disponíveis, que revelou como, em particular, a Confusion Assessment Scale in the Intensive Care Unit (CAM-ICU) é adequada para o SU. Assim, explorou-se a CAM-ICU (versão em português europeu) no SU. Os dados foram registados de forma aleatória e prospectiva numa amostra de conveniência de doentes do SU do Hospital de Braga. Para o processo de validação, a referência foi uma avaliação psiquiátrica. No geral, a CAM-ICU foi um instrumento prático para a avaliação do delirium no cenário real de um SU, mostrando sensibilidade, especificidade e precisão para o diagnóstico de delirium. No seu conjunto, os resultados suportam a viabilidade de um instrumento de avaliação do delirium no SU, juntamente com escores de risco simples que poderão futuramente ser aplicáveis no SU.

Palavras-chave: CAM-ICU, Cuidados Críticos, Delirium, Estados Confusionais, Serviço de Urgência.

Screening and Diagnosis of Delirium in The Emergency Department - a Case Study in Hospital de Braga

ABSTRACT

Delirium is a common neurobehavioral syndrome considered to be caused by a dysregulation of baseline neuronal activity secondary to systemic disturbances. In the hospital setting, particularly in the Emergency Department (ED), delirium is a risk factor for clinical complications, a longer length of stay and discharge to a post-acute nursing facility. Regarding long-term outcomes there is evidence that delirium episodes are associated with poorer outcome, independently of age, sex, comorbid illness or illness severity, and baseline dementia. Nonetheless, delirium remains a major unrecognized problem in the ED. The first step in delirium management, in any hospital setting, is to perform a timely and accurate diagnosis, preferably via the use of a brief (validated) instrument that assesses features in the Confusion Assessment Method algorithm. The assessment of delirium may, nevertheless, be rendered difficult in the ED due to the intrinsic characteristics of the setting. In the present thesis we aimed to firstly frame delirium in terms of historical context and pathophysiology, in a state-of-the-art approach, with particular focus in emergency care. Then, we explored risk and clinical-outcome indicators of delirium in the Emergency Department Intermediate Care Unit (EDIMCU) of Hospital de Braga, in an observational prospective study. Notably, delirium was associated with longer length-of-stay and poor outcome at 1-month post discharge. Next, a literature review on the actual knowledge on available delirium screening tools was conducted, which revealed how in particular the Confusion Assessment Scale in the Intensive Care Unit (CAM-ICU) is suitable for the application in the ED. Thus, the applicability of the CAM-ICU, European Portuguese version, in the ED, was then explored. Data were randomly and prospectively recorded in a convenience sample of patients in the ED of Hospital de Braga. For the validation aspect, the reference standard was a psychiatric evaluation. Overall, CAM-ICU was a practical instrument for the assessment of delirium in the real setting of an ED showing sensibility, specificity and accuracy for delirium diagnosis. Altogether, the results support the evidence of the feasibility of implementing a delirium assessment tool in the ED, along with the operationalization of simple risk scores which could in the future be applicable in the ED.

Key Words: CAM-ICU, Confusional States, Critical Care, Delirium, Emergency Department.

TABLE OF CONTENTS

ACKNOWLEDGMENTS iii

RESUMO v

ABSTRACT vi

TABLE OF CONTENTS vii

LIST OF ABBREVIATIONS xi

GLOSSARY xii

LIST OF FIGURES xvi

LIST OF TABLES xvii

CHAPTER I 1

DELIRIUM AND DELIRIUM IN THE EMERGENCY DEPARTMENT: STATE OF THE ART 1

Introduction 2

1.Framing Delirium Definitions 4

1.1. From Shakespeare's accounts to a modern definition of delirium 4

1.2. Delirium terms across history 8

1.2.1.Ancient times to medieval times – passions can be inflamed, but can the mind suffer from inflammation? 8

1.2.2.18th and 19th Centuries – definitions vary across ages, but some uniformity emerges 11

1.2.3.20th Century – Modern Era where neurophysiology meets the mind 11

1.3. The Diagnostic and Statistical Manual (DSM) and the International Classification of Diseases (ICD) era until present time 13

2. Epidemiology, Pathophysiology and Brain Functional Correlates of Delirium 19

2.1. Epidemiology 19

2.1.1. Risk and vulnerability factors 19

2.1.2. Prevalence and etiologic subtypes 21

2.2. Overview of delirium pathophysiology 30

2.2.1. Degenerating brain vulnerability 31

2.2.1.1. Disrupted cerebral metabolism 33

2.2.1.2. Cerebral Glucose Metabolism 34

2.2.1.3. Cerebral oxygen metabolism and cerebral hemodynamics 35

2.2.1.4. Neuroinflammation and oxidative stress 36

2.2.1.5. Drugs and neurotransmitter dysregulation 37

2.2.1.6. Neuroanatomical substrates and failure of network connectivity 40
2.2.1.7. Other mechanisms 40
2.3. The problem of "Gold Standard" for delirium 41
3. The Problem of Defining Delirium in the Emergency Department 42
3.1. Framework of the ED 42
3.1.1. Structuring and functioning of the Portuguese ED 42
3.1.2. Brief note on observational units within the ED 44
3.2. Translating delirium research into action 44
3.2.1 Improving research in the ED, how do we get there? 44
3.3. The problem of delirium in the ED 48
4. Delirium Treatment in the ED 49
4.1. Punch Line 58
References 59
CHAPTER II 88
RISK AND CLINICAL-OUTCOME INDICATORS OF DELIRIUM IN AN EMERGENCY DEPARTMENT INTERMEDIATE CARE UNIT (EDIMCU):AN OBSERVATIONAL PROSPECTIVE STUDY 88
Abstract 90
Backgrounds 91
Methods 92
EDIMCU 92
Patients and study design 92
Data collection and study design 93
Statistical analysis 94
Results 95
Baseline characteristics and delirium clinical outcome 95
Biochemical parameters 97
One-month outcomes and multivariate analysis 98
Discussion 99
Conclusions 101
Key messages 101
References 104

CHAPTER III **108**

DELIRIUM DIAGNOSTIC AND SCREENING INSTRUMENTS IN THE EMERGENCY DEPARTMENT: AN UP-TO-DATE SYSTEMATIC REVIEW **108**

Abstract: 110

1. Overview 110

2. Literature Review 112

3. Delirium Screening Instruments in the ED and/or in Acute Care Units 120

3.1. Confusion Assessment Method (CAM) 120

3.2. Modified Confusion Assessment Method for the Emergency Department (mCAM-ED) 120

3.3. Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) 121

3.4. Delirium Triage Screen (DTS) 121

3.5. Brief Confusion Assessment Method (bCAM) 121

3.6. Neelon and Champagne Confusion Scale (NEECHAM) 122

3.7. Richmond Agitation Sedation Scale (RASS) 122

4. Concluding Remarks 122

References 126

CHAPTER IV **132**

THE CONFUSION ASSESSMENT METHOD FOR INTENSIVE CARE UNIT: A LARGE COHORT VALIDATION STUDY IN THE EMERGENCY DEPARTMENT OF A TERTIARY HOSPITAL **132**

Resumo: 134

Palavras-chave: 134

Abstract: 135

Keywords: 135

Introduction 136

Methods 137

CHARACTERIZATION OF THE EMERGENCY DEPARTMENT 137

STUDY POPULATION AND DESIGN 138

MEASUREMENTS 139

STATISTICAL ANALYSIS 139

Results 140

Discussion 144

LIMITATIONS 146

Conclusion 147
Declaração de Contribuição / *Contributorship Statement*: 147
Responsabilidades Éticas 147
Ethical Disclosures 148
REFERENCES 149
CHAPTER V **152**
GENERAL DISCUSSION, FUTURE PERSPECTIVES AND CONCLUSION **152**
1.General Discussion 153
2. Future Directions 158
2.1. Tools to Estimate Risk and Machine Learning 158
2.2. Cognitive impairment and Delirium 160
2.3. Pathophysiologic mechanisms 161
3. Conclusions 162
References 163

LIST OF ABBREVIATIONS

β – Beta

A

APACHE II: Acute physiology and chronic health evaluation II

C

CAM-ICU: Confusion assessment method for the intensive care uni

CI: Confidence interval

CBF – Cerebral Blood Flow

D

DSM: Diagnostic and Statistical Manual of Mental Disorders

E

ED: Emergency department

EDIMCU: Emergency department intermediate care unit

I

ICU: Intensive care unit

IMCU: Intermediate care unit

IQR: Interquartile range

L

LOS: Length of stay

R

RASS: Richmond agitation-sedation scale

Q

qSOFA: Sequential Organ Failure Assessment

S

SAD: Sepsis Associated Delirium

SD: Standard deviation

SIRS: Systemic inflammatory response syndrome.

SU: Serviço de Urgência

GLOSSARY

A

Accuracy: The accuracy of a test is its ability to differentiate the patient and healthy cases correctly. To estimate the accuracy of a test, we should calculate the proportion of true positive and true negative in all evaluated cases. Mathematically, this can be stated as: Accuracy=TP+TN/ TP+TN+FP+FN (Baratloo 2015).

C

Cognitive impairment: refers to problems people have with cognitive functions such as thinking, reasoning, memory, or attention (Roy 2013).

Coma: alteration of consciousness that represents the final pathway of various pathophysiological processes in disease states (trauma, toxic-metabolic, vascular, neoplastic, seizures) ultimately leading to derangement in cerebral function manifesting as decreased arousal and awareness (Kornbluth 2011).

Confusion Assessing Method: a standardized evidence-based tool that enables non-psychiatrically trained clinicians to identify and recognize delirium quickly and accurately in both clinical and research settings. The CAM includes four features found to have the greatest ability to distinguish delirium from other types of cognitive impairment (McCabe 2003).

D

Delirium: a clinical syndrome characterized by a disturbance in attention and cognition with acute onset and fluctuating course (Fong 2022).

Dementia: refers to a progressive loss of a previously acquired cognitive skill and can be used as an umbrella term for many types of progressive cognitive decline (Fong, Inouye 2022).

Diagnostic and Statistical Manual of Mental Disorders: a classification system of mental disorders with associated criteria fashioned to facilitate more reliable diagnoses of psychiatric disorders (Miyazaqui 2017).

H

Hemodynamics: the physical study of flowing blood and of all the solid structures (such as arteries) through which it flows (Secomb 2016).

Hemodynamic congestion: volume overload and increased filling pressures and may precede the onset of clinical congestion by days or weeks. Clinical congestion is characterized by progressive dyspnoea, weight gain, and signs of systemic venous congestion (Ilieşiu 2022).

International Classification of Diseases: the international standard diagnostic classification for all general epidemiological, health management purposes and clinical use (https://www.datadictionary.nhs.uk/supporting_information/international_classification_of_diseases__icd_.html).

L

Likelihood ratio: The Likelihood Ratio (LR) is the likelihood that a given test result would be expected in a patient with the target disorder compared to the likelihood that that same result would be expected in a patient without the target disorder (https://www.cebm.ox.ac.uk/resources/ebm-tools).

M

Machine learning: Machine learning is a branch of artificial intelligence and computer science which focuses on the use of data and algorithms to imitate the way that humans learn, gradually improving its accuracy (https://www.ibm.com/cloud/learn/machine-learning).

Medical screening: the systematic application of a test or inquiry to identify individuals at sufficient risk of a specific disorder to benefit from further investigation or direct preventive action (these individuals not having sought medical attention on account of symptoms of that disorder) (Wald 2020).

N

Negative predictive value: The likelihood that a person who has a negative test result indeed does not have the disease, condition, biomarker, or mutation (change) in the gene being tested. The negative predictive value is a way of measuring how accurate a specific test is. Also called NPV. (https://www.cancer.gov/publications/dictionaries/cancer-terms/def/negative-predictive-value).

Neurophysiology: a branch of neuroscience that is concerned with the normal and abnormal functioning of the nervous system, including the chemical and electrical activities of individual neurons (https://dictionary.apa.org/neurophysiology).

Neuroinflammation: an inflammatory response within the brain or spinal cord mediated by the production of cytokines, chemokines, reactive oxygen species, and secondary messengers. These mediators are produced by resident CNS glia (microglia and astrocytes), endothelial cells, and peripherally derived immune cells (DiSabato 2016).

O

Outcomes: also called events or endpoints are variables that are monitored during a study to document the impact that a given intervention or exposure has on the health of a given population (Ferreira 2017).

P

Positive predictive value: The likelihood that a person who has a positive test result does have the disease, condition, biomarker, or mutation (change) in the gene being tested. The positive predictive value is a way of measuring how accurate a specific test is. Also called PPV (https://www.cancer.gov/publications/dictionaries/cancer-terms/def/positive-predictive-value).

Prevalence: a measure of the total number of people in a specific group who have (or had) a certain disease, condition, or risk factor at a specific point in time or during a given period of time (https://www.cancer.gov/publications/dictionaries/cancer-terms/def/prevalence).

R

Risk factor: a clearly defined behavior or constitutional (e.g., genetic), psychological, environmental, or other characteristic that is associated with an increased possibility or likelihood that a disease or disorder will subsequently develop in an individual (https://dictionary.apa.org/risk-factor).

S

Sensitivity: The sensitivity of a test is its ability to determine the patient cases correctly. To estimate it, we should calculate the proportion of true positive in patient cases. Mathematically, this can be stated as: Sensitivity=TP/TP+FN (Baratloo 2015).

Specificity: The specificity of a test is its ability to determine the healthy cases correctly. To estimate it, we should calculate the proportion of true negative in healthy cases. Mathematically, this can be stated as: Specificity=TN/TN+FP (Baratloo 2015).

LIST OF FIGURES

CHAPTER I

Figure 1 Mining foreman R. Thornburg shows a small cage with a canary used for testing carbon monoxide gas in 1928 2

Figure 2 Risk factors for delirium**.** 20

Figure 3 Non-pharmacological approach to agitation in the ED, the TADA approach. 51

CHAPTER II

Figure 1 Patients meeting inclusion and exclusion criteria. 95

CHAPTER III

Figure 1 Flow diagram of the literature review 113

CHAPTER IV

Figure 1 Flow chart of the study sample selection. 140

CHAPTER V

Figure 1 Novel clinical protocol for emergency department management of delirium in older adults (Adapted from: Rosen et al., 2015) 155

LIST OF TABLES

CHAPTER I

Table 1 Synonyms for delirium (Adapted from Francis & Kapoor, 1990)..... 13

Table 2 A comparison of DSM-IV and DSM-5 criteria for delirium 16

Table 3 Etiologic subtypes based on psychomotor features..... 24

Table 4 Symptom clusters and discret mechanistic subphenotypes incorporating the pathophysiology of delirium and integrating interventions..... 26

Table 5 Potential mechanisms associated with the increased risk of delirium in the elderly. 32

Table 6 Practical approach for confusion and agitation in the elderly in the Emergency Department – ADEPT. 53

Table 7 Pharmacology therapy reserved for agitation with delirium 57

CHAPTER II

Table 1 Patient demographics and characteristics stratified by delirium status 96

Table 2 Delirium status classified by delirium subtype 97

Table 3 Biochemical parameters stratified by delirium status..... 98

Table 4 Clinical outcome and mortality at one-month assessment and multinomial logistical regression analysis results..... 99

CHAPTER III

Table 1 Summary of studies using delirium screening tests. 114

Table 2 Summary of the psychometric aspects of validated delirium screening instruments 119

CHAPTER IV

Table 1 Patient characteristics stratified by delirium status assessed using CAM-ICU..... 141

Table 2 Patient characteristics stratified by evaluation. 142

Table 3 Patient characteristics stratified by delirium status assessed using both the CAM-ICU and the DSM-5 by psychiatrist assessment. 143

Table 4 Diagnostic performance of the CAM-ICU. 144

Table 5 A comparison of the CAM-ICU and the DSM-5. 144

CHAPTER I

Delirium and delirium in the emergency department: state of the art

Introduction

Delirium is a common neurobehavioral syndrome, particularly in acute and long-term care settings, considered to be caused by a dysregulation of baseline neuronal activity secondary to systemic disturbances (Maldonado, 2008). It affects one third of hospitalized elders, and three quarters of all adults, in the intensive care unit (ICU) and in palliative care (E. R. Marcantonio, 2017). Moreover, it can be found in up to 70% of patients with sepsis syndrome, correlating with sepsis severity (Burkhart et al., 2010). It is, thus, a serious medical condition requiring immediate investigation and management (Boucher et al., 2019). Despite this, and like the use of canaries in coal mines to detect carbon monoxide and other toxic gases before they could hurt humans, delirium may occur before failure of other organs and thus be either preventable in its onset or ramifications (Figure 1). Thus, and considering that delirium was one of the first mental disorders to be described by medical writers (Lipowski, 1991), why are we still looking at it as if it barely existed?



Figure 1 Mining foreman R. Thornburg shows a small cage with a canary used for testing carbon monoxide gas in 1928 (From: Smithsonian)

Delirium is a clinical diagnosis, however studies comparing clinical documentation with research assessments suggest that only 12 to 35% of delirium cases are recognized (Inouye et al., 2014; E. R. Marcantonio, 2017). Although, the clinical relevance of delirium has led to the development of best practice guidelines by important scientific societies, such as the American Psychiatric Association, the British Geriatrics Society, and the National Institute of Clinical Excellency (NICE), it still lags far behind

other important public health-care issues (Khachaturian et al., 2020; Wilson et al., 2020; Cerejeira et al., 2011). The problem is amplified by the fragmentation of care of sicker patients across a variety of venues, challenging clinicians to identify and manage delirium efficiently across a wide variety of settings (Francis & Young, 2021). This leads to an even bigger problem when linking delirium to specific high-turnover settings, namely the Emergency Department (ED). In fact, in the ED, delirium is missed 57% to 83% of the time mainly because ED providers do not routinely screen for this syndrome (Han & Suyama, 2018). Why? Foremost because, in the ED, and/or intermediate or acute care units (EDIMCU) within it, much of the problem regarding delirium incidence and prevalence relates, in great part, to the unique environment: intense time demands on providers and high volume of patients. Together, these aspects can both (i) render the care for at-risk groups (such as older adults) challenging, and (ii) hinder the use and validation of (delirium) screening tools (Mariz et al., 2016). Second, and not less pertinent, defining delirium, and thus actually diagnose it with certainty, is complex. Currently, there is no definitive diagnostic test for delirium; hence, detection of delirium must rely on eliciting key clinical features using a combination of patient interview, cognitive testing, observation, and informant history (Oh et al., 2020). So, identifying which practices best apply to a specific setting, and how to deliver it in a standardized, high-quality, and sustainable way, is still a major focus of delirium research (E. Marcantonio, 2019). Herein, we propose to:

1. Explore the relationship between delirium onset in an EDIMCU and patient outcome after discharge. For this, delirium occurrence among patients admitted to the EDIMCU at the Hospital de Braga (Braga, Portugal) was addressed;
2. Validate a screening tool adapted to a specific reality specifically in the ED at the Hospital de Braga (Braga, Portugal);
3. Assemble a bundle of harmonized delirium measures that could be applied and refined within the ED.

Thus, in this introductory chapter, we first provide a historical perspective on the topic of delirium (and its definition), followed by a scrutiny of problems with the unification of terminology, and a brief update on epidemiology and pathophysiologic aspects of delirium, with a focus on cerebral functional correlates. This is followed by a consideration of “the problem of a gold-standard” to assess delirium, and, upon a contextualization of delirium in the ED, and a brief oversight of the problem of translating research into a specific environment, a summary review of pharmacological and non-pharmacological treatment of delirium, funneled down to the ED setting, before final remarks.

1.Framing Delirium Definitions

1.1. From Shakespeare's accounts to a modern definition of delirium

No else but Shakespeare could tell, in words and images, the deepest mechanisms of the human mind: 'He was not of an age, but for all time!' (Bates, 1978). For days to come, Shakespeare told us in a unique, yet universal, way, the maladies and "The pangs of dispriz'd love" (Hamlet 3.1.73), placing Hamlet as the most brilliant ratiocinator of the soul, but the lamentable lover (RAVASSAT, 2006). We thus link Shakespeare to all ventures regarding human real feelings, calling him the Soul of the Age, but, curiously, The Bard was well beyond the boundaries of common knowledge and vocabulary. The extensions of his observations, and the way represented on stage, are well known in Law sciences, as Lord Penzance quoted: "a knowledge [of the law] so perfect and intimate that he was never incorrect and never at fault" (F. Davis, 2000). Yet the extension of what we are talking about goes beyond the laws that "rule" human relations and insinuates itself through the matters of biological kinds of laws that rule the equilibrium between health and disease. His knowledge on medical terms has been discussed by scholars since the 18th century (F. Davis, 2000; López-Valdés et al., 2018). More impressive than the fact that more than 700 medical references are recorded in Shakespeare's plays (Gomes, 2015), is that, at Shakespeare's time, true medical literature, like medicine itself, was still in its infancy, so that it would not have been possible for Shakespeare to have absorbed much from reading what was available to him in English (F. Davis, 2000). Moreover, The Bard described the symptomatology of some of his characters that fulfill diagnostic criteria for several neurological nosologies, such as parkinsonism, epilepsy, sleeping disturbances, dementia, headache, prion disease, and paralysis (Gomes, 2015). But no account of "Shakespearean Neurology" is complete without reference to his observations of delirium (Fogan, 1989; Lindesay, 1999). Although he did not use modern terms for the "abnormal" character profile, Shakespeare described what we know today as various neurological symptoms, signs, and courses of disease (Paciaroni & Bogousslavsky, 2013). Shakespeare showed us "All the world's a stage, and all the man and woman merely players" (As You Like It 2.7.146-147), describing the seven stages of a man's life, and using this as a vehicle for a secondary theme concerned with the effect of age and ageing on the prevalence of mental disorders and how various stages of life may govern the form and content of their presentation (Trethowan, 1988). Despite the paucity of medical literature in the Elizabethan time, there have been suggestions that Shakespeare had acquaintance with the *A Treatise of Melancholy*, published in 1586 by Thimothy Bright (W. M. M., 1940), a resident physician of St Bartholomew's Hospital, in London (Kail, 1986).

Probably, he drew on the information from this book to create his psychological (and physiological) delineations. Of these there are many, but here we'll focus on an example of incredible wit and deep attention of description, for the matters that most count for this introduction:

A parted ev'n just between twelve
and one, ev'n at the turning o'th'
tide I saw him fumble
with the sheets, and play with
flowers, and smile upon his finger
ends, I knew there was but one
way; for his nose was as sharp as
a pen, and 'a babbled of green
fields... A bade me lay more
clothes on his feet. I put my hand
into the bed and felt them, and
they were as cold as any stone.

(Shakespeare W. *Henry V*, Act II, III:12-17, 21-23 (1600))

This is an account from Mistress Quickly, describing what it seems like Falstaff's "quiet" delirium (Lindesay, 1999). But, as with every masterpiece in drama, what is not said is as important as what it is said, and Falstaff's delirium account shows us, modern clinicians, the unknown histories and phenomenology of a medical encounter, where the source of information must come from friends and relatives (Lindesay, 1999). Falstasff had been a page in the Norfolk household some fifty-five years before, and as pages usually commenced at the age of seven, he must have been over sixty-five (Kail, 1986). So, thinking in terms of drama, we travel from Pages to Knights and Kings, thinking of illness in relation to age independently of social status, but with an underlying age factor. In fact, age is probably the most important risk factor of disease (Harman, 1991; Harman, 2001; Niccoli & Partridge, 2012; Franceschi et al., 2018; Hou et al., 2019; Oliveira J E Silva et al., 2020). In Winter's Tale, Polixens, the

King of Bohemia, disguised himself and endeavored to find out his son's opinion of an old man. He asks his son Prince Forizel:

Polyxenes. Methinks a father

Is at the nuptial of his son a guest

That best becomes the table. Pray you, once more,

Is not your father grown incapable

Of reasonable affairs? Is he not stupid

With age and alt'ring rheums? Can he speak, hear,

Know man from man, dispute his own estate?

Lies he not bed-rid, and again does nothing

But what he did being childish?

The young Florizel replies, describing the ideal situation when an old person should be fit and in full possession of his faculties:

Florizel. No, good sir;

He has his health and ampler strenght indeed

Than most of his age.

(Shakespeare W. *The Winter's Tale*, IV, iv: 386-394 (1610))

Here, we are directed to the important fact of knowing the basal condition of the patient in the moment of assessing an illness/clinical condition, as is delirium (Gibb et al., 2020). As Polixenes, many patients/caregivers seek advice about how to determine when cognitive changes are normal versus not normal; where, knowing the baseline cognitive function of the person is crucial (Khachaturian et al., 2020). From Shakespeare we can explore a powerful idea: one of the most effective ways for clinicians to understand these issues, and for patients and their family members to convey suspected delirium to their clinicians, is to formalize the approach by which patients, family members, and their clinicians, tell stories (Gee, 2016; Khachaturian et al., 2020).

This is quite common in drama, where the actor portrays an impersonation, questioning the audience what it could be and using disguise to reach the truth. Sometimes the actor goes off stage, creating a sense of strangeness in the audience, testing the boundaries of what is real and what is fiction. To be normal, in theater, is to accept the "suspension of disbelief", a concept coined by Samuel Taylor Coleridge in 1817 (and the reason because we don't run out of the movie theater when a monster shows up on screen) (Meyer, 2005). This is not unlike delirium, where the patient, often, presents an "altered strangeness" to himself and others. In fact, the term "delirium," deriving from the Latin "deliro-delirare", and meaning "offtrack," was accepted to be firstly used by Celsus in the first century A.D. (Isik & Grossberg, 2018). It evokes the acceptance that the "suspension of disbelief" is broken, whereas the brain runs off the theater screaming for monsters that do not exist.

From Shakespeare, we move towards a routed tradition in medicine, where recognition of features, defining the syndrome, identification of tissue pathology, demonstration of pathogenesis, and discovery and development of cures and treatments (Stevens & Price, 2014), are stages of development common to each medical science. For the sake of The Bard, delirium is barely in the beginning of each of these developmental stages. Moreover, the heterogeneity of terminology that has been used across the history of medicine is also reflective of the peripheral status which delirium has been given. However, the lack of standardized terminology also reflects the heterogeneity of its phenotype and its temporal manifestation. It is quite difficult to reach to the molecular level the understanding of some mechanisms of the mind, and, losing our grip on the above mentioned first two stages of medical tradition, we are still trying to frame the features, and define the complex and rich phenomenology of delirium. But in the pages of history, delirium was, and still is, a clinical diagnosis, and this could be the best explanation of the continuum between delirium and "normality" (Isik & Grossberg, 2018).

One of the principal problems that are posed to delirium research is the lack of standard diagnostic criteria, for, when it is present, the data of epidemiological studies gets more accurate (D. H. J. Davis et al., 2013). Currently, delirium is poorly recognized, in part because of lack of a unifying definition, a lack of education, and a lack of consistent application of clinically effective assessment tools (Khachaturian et al., 2020). Here, we start to address this issue by first offering a historical perspective on how words and terms used to describe delirium have evolved with medicine.

1.2. Delirium terms across history

1.2.1. Ancient times to medieval times – passions can be inflamed, but can the mind suffer from inflammation?

Delirium is ranked among one of the first mental disorders to be described by medical writers (Lipowski, 1991). However, there is a myriad of mutations that have occurred throughout our recorded history (of delirium). Few authors, beyond Lipowski, have studied the evolution of the term (Isik & Grossberg, 2018). Lipowski, who worked and wrote extensively on delirium (Lipowski, 1991), is regarded as the father of modern research into this condition (Adamis et al., 2007). Particularly, he has remarked on the terminological chaos that has characterized delirium's history from ancient times to the present day (Lindesay, 1990, 1999). His work has had profound implications in medical knowledge, although it is far from acknowledging every aspect of delirium. In fact, delirium is still considered, to the present day, an unclear and unrecognized disorder (Deksnytėet al., 2012).

But, let us start from the beginning. Early Greek and Roman medical writers knew that febrile and toxic illnesses could be accompanied by abnormalities in perception, cognition, behavior, and mood, identifying two basic patterns of presentation: the agitated form (*phrenitis*) and the form distinguished by inactivity and sleepiness (*lethargus*) (Rabinowitz, 2002). There are many descriptions of what we would recognize as delirium in the Hippocratic writings, particularly in the books of Epidemics (Lindesay, 1999), thus dating back almost 2,500 years. Hippocratic texts do not refer specifically to delirium, as this is a Latin word, and all Hippocratic body of knowledge was written in Greek; however, it is in the Hippocratic writings where first are described conditions of phrenitis and paraphrenitis, which are now perceived as a somatic type of delirium and referred to variously expressed acute behavioral disturbances that manifest during bodily inflammation (Deksnytėet al., 2012). Phrenitis, which literally means inflammation of the mind or diaphragm (Gk *phren* = mind, diaphragm; *itis* = inflammation), is an ancient disease concept denoting a disease consisting of a combination of a mental disorder and fever. So, for centuries, physicians had noticed the importance of fever to distinguish phrenitis from conventional "madness". In ancient literature, the concept was even somewhat broader and meant the association of mental disease and physical illness. Hippocrates was, thus, further describing phenomenology. The term phrenitis described an agitated form of the disturbance, characterized by excitement and insomnia, but he also used the term lethargus to define the form distinguished by inactivity and sleepiness. He believed that lethargus could turn into phrenitis and back again into lethargus (Adamis et al., 2007; Deksnytėet al., 2012). This splitting up of what would eventually be

regarded as variants of a single condition persisted for almost two thousand years (Rabinowitz, 2002). Nonetheless, it is worth noting that Hippocrates used about sixteen different words, besides φρενιτις (phrenitis) and ληθαργος (lethargus), to refer to and name the clinical syndrome which we now call delirium, such as ληρος (leros), μανια (mania), παραφροσυνη (paraphrosyne), and παραληρος (paraleros). It is difficult to find the exact meaning of these terms; for example, the term παραφροσυνη (paraphrosyne) can be used as meaning of madness, but it can also mean a decline in, or a loss of, consciousness (Adamis et al., 2007).

In summary, Greek and Roman writers recognized three main forms of such disorders: mania, melancholia, and phrenitis or delirium. Like many diagnoses, phrenitis was (later) reconceptualized and repackaged rather than simply discarded. That the original Greek embraced both mental and physical symptoms is a reminder of the perennial psychosomatic nature of medical practice (Bynum, 2000). Moreover, the distinction between impaired consciousness and madness in the Hippocratic texts was not a major concern for the authors because they mostly disregarded madness, and mainly focused on what now we call delirium (Diego & Atlas, 2020). Withdrawal alcohol syndrome (i.e. delirium tremens), as an example, is known from antiquity, and although first described in 1813 by modern physicians it had already been identified by the Roman African (and early Christian) medical writer Cassius Felix in the 5th century A.D., drawing heavily on ancient Greek sources (Charlier & Prêtre, 2006; Deksnytė et al., 2012). An apparent uniformity of nomenclature during antiquity may, thus, be due to the translation of many distinct words to 'delirium' in English (Adamis et al., 2007).

From here, the term "delirium" was first used by Celsus in the 1st century A.D., but on the whole the word "phrenitis" was used more often in the ancient medical literature (Lipowski, 1991). The word delirium derives from the Latin "deliro-delirare" (de-lira, "to go out of the furrow") – hence, to deviate from a straight line, to be crazy, deranged, out of one's wits, to be silly, to dote, to rave (Adamis et al., 2007; Slooter, 2017). It is noteworthy to highlight that during this period some new diseases were incorporated into the nosological treatises, such as melancholia and mania, and an important aspect was to separate them from delirium (Diego & Atlas, 2020). Aretaeus was, in this respect, an author from the 2nd century A.D. whose work aimed to distinguish *phrenitis* from other forms of mental conditions (particularly, from melancholia and mania).

After a considerable iatum in delirium references in the medical literature, during the 16th century more writings appeared on phrenitis and delirium. 'Paraphrenesis' reappeared as a term to distinguish

delirium caused by fever, but it was also used by Guainerio to describe a pre-delirious phase (Adamis et al., 2007). An important contribution came from a barber-surgeon, Ambroise Paré, in the 16th century. As a field surgeon in numerous battlefields for the king in Italy and France, Paré had performed many successful operations on the skull, which later appeared in the title page of his extensive *Les Oeuvres de M. Ambroise Paré* (Finucci, 2021). So, the occurrence of so called "delirium traumaticum" or "delirium nervosum" has been known to surgeons since or before the time of Ambroise Paré, though, his originality was to describe delirium as a transient condition that commonly followed fever and pain due to wounds, gangrene, and operations, involving severe bleeding of the patient (Adamis et al., 2007). Thus, the first-time delirium is used is by no means consensual. In English literature we only have the studies from Lipowski. According to Lipowski, the first description of delirium in the English medical literature appeared in Barrough's textbook *The Method of Physick*, first published in 1583 (Lipowski, 1991). Interestingly, the advances in this period come from a more accurate clinical description, and following the example from Barrough, he referred to delirium as "Frenesie" and observed that it involved the derangement of three main functions – imagination, cogitation, and memory – and, originally, it also featured disturbed sleep (Lipowski, 1991). This is an important breakthrough, having the core clinical features of delirium defined in the 16th century, some centuries before the Diagnostic and Statistical Manual of Mental Disorders (DSM) definition.

Later on, an interesting contribution to the concept of delirium was made by Thomas Willis in the 17th century. Thomas Willis is probably the founder of clinical neuroscience (Molnár, 2004), with most of his practice revolutionizing the way we approach medical science. One important aspect of his medical praxis was that he often followed his patients for years, including dissecting them after their death. It gave him empirical evidence to contest established ideas. For example, he did not accept the idea that an inflammation of the diaphragm could cause 'paraphrenesis' (he had seen an autopsy of an abscess involving the diaphragm, but the patient had not had delirium or para-phrenesis during life) (Adamis et al., 2007). He was, therefore, in a position to relate altered behavior to abnormalities of the brain (Molnár, 2004). He also did not conform with the terminology of his time around delirium, phrenzie, madness, and melancholy (Eadie, 2003). While accepting the current theory at the time, in which delirium and 'frenzy' (phrenesis) differed only in duration of their mental disturbance, he believed that delirium could also occur in conditions which were not accompanied by fever-like "drunkenness" or "hysteria". He had insightful clinical observations regarding the evolution and natural course of the disease, correlating the prognosis of delirium with the nature of the febrile illness, the patient's age and previous health, and that, while delirium may be resolved after the fever settles down, cases of

protracted delirium might lead to 'a state of perpetual raving (madness), to melancholy, or to a state of foolishness and stupidity' (Adamis et al., 2007; Eadie, 2003).

1.2.2. 18th and 19th Centuries – definitions vary across ages, but some uniformity emerges

By the beginning of the 18th century most medical writings distinguished delirium, on the one hand, from phrensy or phrenesis on the other (Adamis et al., 2007). It is both a reminiscence from the Hippocratic legacy and a convergence for a more pathophysiological description of mental disorders. However, there was an established tendency for discordance where the description of delirium offered by the early medical writers was strikingly consistent, the relevant terminology was not (Lipowski, 1991). Nonetheless, from the 18th century, delirium is one of the most encountered mental disorders in general hospital practice. It has been called "everyman's psychosis" to highlight the fact that anybody is potentially susceptible to it (Aita, 1968), and it has been referred to as reversible madness which "no doctor likes to miss" (Lipowski, 1987, 1991).

The 19th century saw the introduction of two new concepts – "clouding of consciousness" and "confusion" – and an attempt was made to distinguish delirium caused by alcohol as a separate condition. Clinical symptoms rather than etiology and prognosis became the focus of definitions (Lindesay, 1999; Adamis et al., 2007). Thus, the 19th century saw a more organic approach, and even the prototypical subclassification of delirium was proposed, as early as in 1892, by the French alienist Philippe Chaslin, which borrowed the term "confusion mentale primitive" from a previous description proposed by Delasiauve during the 1850s (Camus, 2002). There are further interesting connections between the dream experience, delirium tremens and delirium, after Lasegue description of delirium tremens, in which perceptual disturbances were considered as a dream-like experience (Lasègue, 2010).

1.2.3. 20th Century – Modern Era where neurophysiology meets the mind

The 20th century saw an increase in research on the physiopathology of delirium. It was not until the phenomenologically-focused 19th century that the pursuit of a syndrome took over from the attempt at a diagnosis with its prognostic and management implications. In the late 19th century, Emil Kraepelin described, in the early edition textbooks on psychiatry, acute onset psychotic states with delusions, significant mood alterations, and vivid hallucinations that vanished abruptly. The term "period delirium" was introduced in the 4th edition of his textbook (FitzGerald, n.d.). It wasn't, however, until the 20th

century that delirium was marked by a full recovery, which was probably due to the desire for a clear distinction from dementia (Adamis et al., 2007). Although the phenomenology was described in terms of an organic brain syndrome, the terms continued to populate. In 1924, Carl Kleist, following on from the work of Carl Wernicke, coined the term "cycloid psychosis" to describe the phenomena that 'manifest themselves in multiple phases during life, come and go in an autochthonous way, often show antagonistic syndromes - confusion and stupor, hyperkinesis and akinesis - and do not lead to mental defects'. In addition, he described cycloid psychosis in terms of confusional psychosis and motility psychosis. Such descriptions are arguably the same as the modern conception of delirium (FitzGerald, n.d.).

One of the most remarkable developments in the concept of delirium was by Engel and Romano in the 1940s (Engel & Romano, 2004). In fact, modern delirium scholarship owes much to the internist George Engel and psychiatrist John Romano, whose work in the 1940s and 1950s characterized delirium as a "syndrome of cerebral insufficiency." (Engel & Romano, 2004; Oldham & Holloway, 2020). In particular, they (Engel & Romano, 2004) used EEG to investigate delirium and found that it was associated with a reduction of cerebral metabolic rate as indicated by an increase in slow wave activity (Engel & Romano, 2004). The era of delirium neurophysiology had begun.

From here, during the last part of the 20th century, attempts were made to define mental disturbances, including delirium, by consensus, and two classification systems emerged: the DSM (Diagnostic and Statistical Manual of Mental Disorders), of the American Psychiatric Association, and the ICD (International Classification of Diseases). A crucial factor in the development of more standardized concepts (and, subsequently, lines of diagnosis and care) about delirium was demographic change, especially in developed countries, with an increasing proportion of hospital beds being occupied by men and women in their seventies or eighties, often with multiple physical and cognitive problems (Adamis et al., 2007). We, thus, entered an age where the input from psychology and neurosciences permitted evolution in the development stages of medical sciences. Nevertheless, the 20th century was the stage for a schism that only recently has been overtly debated but, still, not completely resolved. Various authors started to point to the urgent need of clarification of the terminology around delirium. This comes along with what has been said above: owing to the accumulation of 2,500 years of myriad mutations, which have occurred throughout our recorded history of delirium, the task of reviewing all the nomenclature was at the very least difficult. Liston identified over 30 terms used in recent literature to denote delirium; a partial listing is given in Table 1 (Francis & Kapoor, 1990).

Table 1 Synonyms for delirium (Adapted from Francis & Kapoor, 1990)

Acute brain syndrome	Exogenous psychoses
Acute cerebral insufficiency	Metabolic encephalopathy
Acute confusional state	Pseudosenility
Acute mental status change	Reversible cognitive dysfunction
Acute organic psychosis	Reversible dementia
Acute organic reaction	Reversible toxic psychosis
Acute organic syndrome	Subacute befuddlement
Agitated confusional state	Toxic confusional state
Altered mental status	Toxic delirious reaction
Cerebral insufficiency syndrome	Toxic encephalopathy
Dysergastic reaction	Toxic-metabolic encephalopathy
	Toxic psychosis

1.3. The Diagnostic and Statistical Manual (DSM) and the International Classification of Diseases (ICD) era until present time

The proper history of the DSM can be intermingled with the history of the term delirium as a diagnostic entity (Tucker, 1999). The DSM was created in 1952, thrived in the first editions to put order in the diagnostic chaos in the American Psychiatric community, and only in 1968 did it make an effort to update the nomenclature and to make it more consistent with ICD-8 (Tucker, 1999). The first attempt to unify the terminology of delirium was the 1980 publication of the third edition of the American Psychiatric Association's Diagnostic and Statistical Manual (*DSM-III*, 1980) with its recent revision (*DSM-III-R*, 1987) introducing a standardized nomenclature and criteria for the diagnosis of delirium (Francis & Kapoor, 1990). These were historical events in the unification of terminology, drawing a deep breath from the two encyclopedic works of the psychiatrist Zbigniew Lipowski, who introduced the unified concept of delirium (Lipowski, 1980, 1990). The DSM-III signaled a great change in American psychiatry, and an even bigger change in the conceptualization of organic brain disorders (Tucker, 1999). Here, clearly delineated for the first time in the formal nomenclature, were delirium, dementia and amnestic disorders, or as Lipowski (Lipowski, 1990) stated so lovingly '...delirium has become established as the designation for the most common and most important acute organic brain syndrome. This development became finally enshrined in DSM-III' (Tucker, 1999).

The DSM-IV introduced a more comprehensive and highly inclusive description of delirium that has become the preferred diagnostic criteria for both clinicians and researchers (Morandi et al., 2013;

Meagher et al., 2014). It was also the first attempt to create a scientifically based psychiatric evaluation for delirium (Wilson et al., 2020). Altogether, these attempts represented a forward progression for simplification and consensus. However, a trend for abbreviation of the essential criteria (Blazer & van Nieuwenhuizen, 2012) and studies, indicate considerable disparity in delirium detection when applying these different DSM versions and the International Classification of Diseases – Tenth Edition (ICD-10), published in 1993 (Cole et al., 2003; Laurila et al., 2004; Cole et al., 2007; Kazmierski et al., 2008, 2010; Thomas et al., 2012). One possible explanation is that the ICD-10 criteria for delirium requires the presence of symptoms from several domains: consciousness and attention, global disturbance of cognition, psychomotor disturbance, sleep–wake cycle disruption, and emotional disturbances. On the other end, both in research and clinical practice, the DSM criteria have been more commonly employed, possibly because the ICD-10 criteria are more restrictive (Cole et al., 2003; Wilson et al., 2020). Some evidence shows that the ICD-10 had the lowest, and DSM-5 had the highest, interrater reliability (Sepulveda et al., 2016). Similar to a previous report of low ICD-10 reliability in general hospital inpatients, ICD-10 criteria generally have the worst reliability values (Malt et al., 1996; Sepulveda et al., 2016).

The important changes that were made from the DSM-IV to the DSM-5 definition is in the account of a rapid change in brain functioning leading not to 'disorganized thinking and/or altered level of consciousness', but instead to 'confused thinking and reduced awareness of the environment', often caused by severe illness and hospitalization. Thus, delirium is now redefined in terms of reduced awareness and inattention, while removing the term 'consciousness' altogether. Such an alteration has been suggested to substantially impact both clinical care and research (Meagher et al., 2014), and it deserved prompt comments from the European Delirium Association (EDA) and the American Delirium Society (ADS) ("The DSM-5 Criteria, Level of Arousal and Delirium Diagnosis: Inclusiveness Is Safer," 2014). Importantly, although no major changes from DSM-IV were made to the core elements of DSM-5 criteria for delirium, there are some differences in content and wording of the criteria (Table 2) that may impact upon the alignment between DSM-5 and previous criteria (Meagher et al., 2014). For example, in DSM-5, the term 'consciousness' is not used at all. Delirium is now more restrictively defined in terms of its cognitive features, and the level of arousal element implicit in prior DSM criteria has been removed. Moreover, Criterion D states that inattention or changes in cognition 'must not occur in the context of a severely reduced level of arousal such as coma' ("The DSM-5 Criteria, Level of Arousal and Delirium Diagnosis: Inclusiveness Is Safer," 2014). The removal of the term 'consciousness', and the focus on reduced awareness and inattention, might substantially narrow the inclusiveness of the

criteria, depending on how strictly this term is interpreted. The application of DSM-5 criteria could impact substantially upon both clinical care and research case identification, such that it is important to understand how they compare in the same patient population (Meagher et al., 2014). However, just how consciousness is impacted in delirium remains uncertain, as reflected in the diverse iterations of the DSM diagnostic criteria. Consciousness itself is currently beyond the reach of a unitary definition, and despite advances in research the neural correlates have proved elusive (Tononi et al., 2016; Eeles et al., 2020).

Acknowledging the cross-specialty importance of delirium, an international panel of experts, representing ten academic societies, recently issued recommendations on the preferred nomenclature of delirium and acute encephalopathy (Oldham & Holloway, 2020; Slooter et al., 2020). The panel discouraged use of the terms “acute confusional state”, “acute brain dysfunction”, “acute brain failure”, and “altered mental status” (Slooter et al., 2020). Thus, the present era in delirium encompasses a more integrative vision, which encourages clinicians to become neuroscientists and neuroscientists to become clinicians (Oldham & Holloway, 2020).

Table 2 A comparison of DSM-IV and DSM-5 criteria for delirium (Adapted from Meagher et al., 2014)

DSM-5	DSM-IV	Comments
A. Disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).	**A.** Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention.	The cardinal criterion for DSM-5 and DSM-IV includes both inattention and reduced awareness of the environment. Although attention and awareness are important components of normal consciousness, they do not fully represent it. The suggestion that orientation to the environment indicates awareness is new to DSM-5.
B. The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity the course of a day.	**B.** The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.	Both capture acuity of onset and fluctuation of severity. DSM-5 lists examples of other affected cognitive domains with perception. Change from baseline for other cognitive domains is noted in DSM-IV.
C. An additional disturbance in cognition (e.g.memory deficit, disorientation, language, visuospatial ability, or perception).	**C.** A change in cognition or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established or evolving dementia.	Unlike DSM-IV, DSM-5 criteria specifically excludes coma from being labelled as delirium but suggests that where reduced arousal impairs ability to engage with cognitive testing that this can be deemed evidence of severe inattention. Both exclude dementia as the primary cause of the disturbance while DSM-5 more broadly includes other neurocognitive disorders besides dementia.
D. The disturbances in Criteria A and C are not better explained by a pre-existing, established or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.	**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.	DSM-5 has a broader list of etiological types.

Table 2. *Cont.*

DSM-5	DSM-IV	Comments
E. There is evidence from the history, physical examination or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal, or exposure to a toxin, or is due to multiple etiologies.		

Note: Adapted to allow direct item comparison from DSM-IV (American Psychiatric Association, 1994) and DSM-5 (American Psychiatric Association, 2013). DSM-IV, Diagnostic and Statistical Manual fourth edition; DSM-5, Diagnostic and Statistical Manual fifth edition.

More advanced and conceptual sophisticated models are being proposed. The system failure model is one of them, with some parallelism from the studies of large industrial and engineered systems. For many brain disorders, such as dementia and delirium, the use of a systems failure model eschews the unitary etiologic factor or a single cause theory of pathogenesis (Khachaturian et al., 2020). The Systems Integration Failure Hypothesis (SIFH) attempts to explain how the various proposed delirium pathophysiologic theories interact with each other, causing various clinically observed delirium phenotypes. A better understanding of the underlying pathophysiology of delirium may eventually assist in designing better prevention and management approaches (Maldonado, 2008). The SIFH encompasses an integrative approach where multiples causes are intermingled in a network and allow to identify more discriminately where the system fails, such as energy deficiency, region-specific disturbances, direct effect on neurotransmitter systems, and neuro-inflammation, each of which would entail unique treatment considerations to restore network function (Oldham & Holloway, 2020).

In conclusion, illness classifications have been proposed and revised since antiquity, but, for the most part, the essential components have changed very little (Maslove et al., 2022). Nowadays, we've reached the concept of a spectrum, rather than a closed definition, incorporating the insights from both delirium and acute encephalopathy. Thereby, we may call it "Delirium Disorder". Its terminology, which distinguishes between the diagnosis of delirium disorder and the clinical phenotype of delirium, is intended as an analogy to the recently introduced term major neurocognitive disorder for dementia (Oldham et al., 2018, 2022). This has profound consequences both in detection and therapeutics, particularly in the ED. Moreover, the diagnosis of delirium disorder offers a means of unifying the models of delirium and acute encephalopathy (Oldham et al., 2022).

In the next part, we will try to integrate the insights from both delirium and acute encephalopathy, capitalizing on the benefits of each while mitigating against each of their liabilities (Oldham et al., 2018, 2022). This will help in the final proposition of the thesis, with the development of an actuation chart, based on both the experience and the state of the art.

2. Epidemiology, Pathophysiology and Brain Functional Correlates of Delirium

2.1. Epidemiology

2.1.1. Risk and vulnerability factors

There are main pathways that drive causation of delirium as a physiological consequence of a medical condition, substance withdrawal or intoxication state, exposure to toxins, or a combination of these. However, this might be looked at as a simplistic point of view, where, summarizing the complex problem of risk and vulnerability of delirium, is a means to be proactive in a busy environment such as the ED. Delirium is, thus, determined by a balance between background characteristics of patients and precipitants that should be clearly stated (Wilson et al., 2020). Overall, delirium can be practically seen as a marker of vulnerability in older people (Bellelli et al., 2021). However, this doesn't mean that delirium develops only in the older/elder population, as, for example, even in patients with apparent little or no vulnerability to developing delirium, the physician should be highly concerned for an underlying life-threatening illness (S. Lee et al., 2021). This entails a yet undisputed view based on the interaction of premorbid factors, factors relating to presenting illness, and post-admission factors (Wilson et al., 2020) (Figure 2).

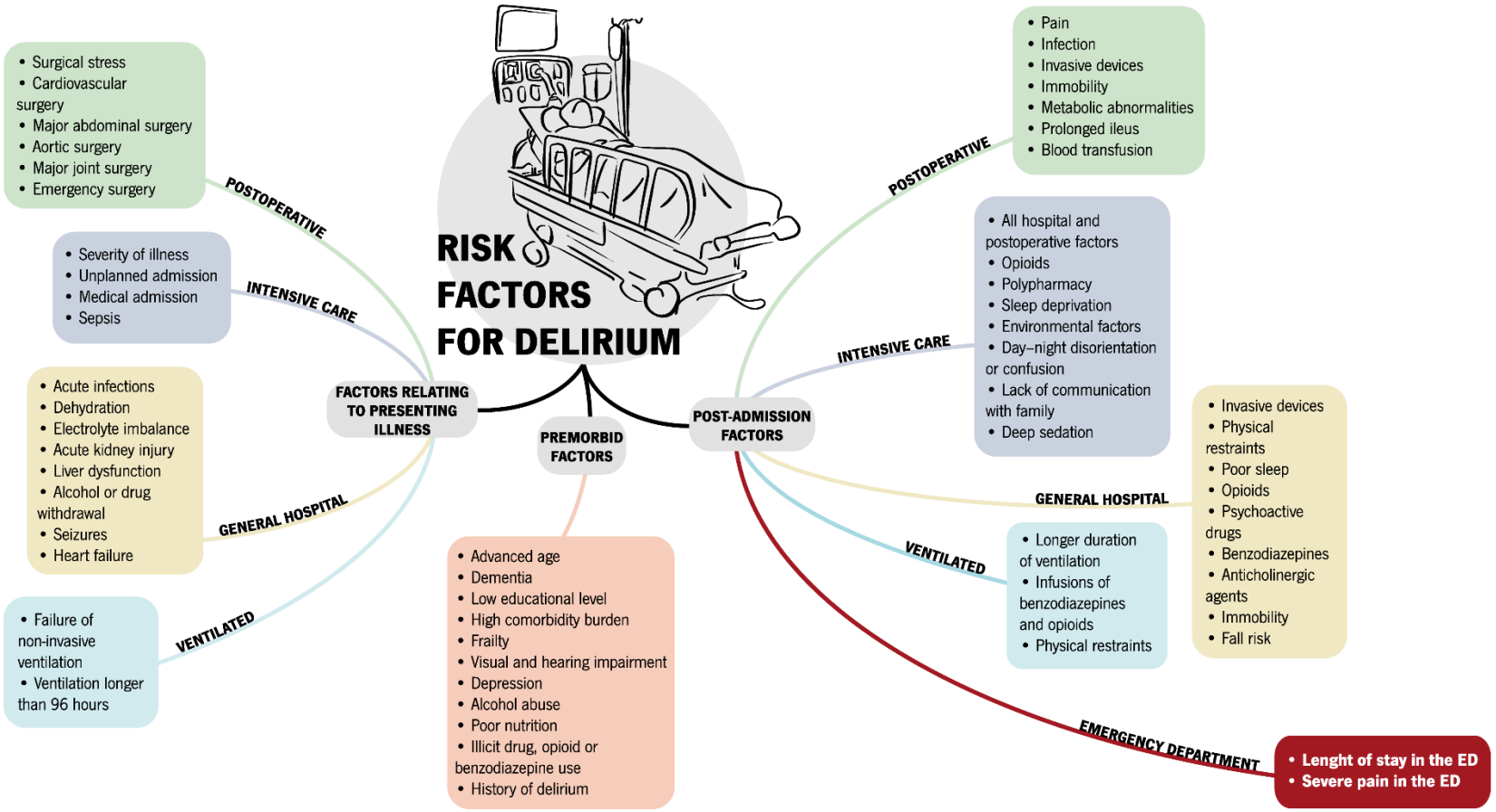


Figure 2 Risk factors for delirium**.** Risk factors for delirium relate to premorbid or predisposing factors (that is, a patient's characteristics) and to precipitating factors, which are factors relating to the presenting illness or that occur after hospital or intensive care unit admission. There is a lack of evidence that demonstrate specific factors for the ED, besides length of stay and severe pain. (Adapted from: Oliveira J. e Silva et al., 2021; Wilson et al., 2020)

This undisputed view has been challenged by a refining of the definition of delirium, as we pointed out earlier, trying to integrate what is one of the less understood topics: that is, if delirium should be studied regardless of phenotype or causation, but instead as broader group of various types of deliria with discrete physiological conditions (Oldham et al., 2018; Wilson et al., 2020). The purpose of refining the definition of delirium goes beyond a formal categorization stimulus, but, instead, has implications on research and treatment (Oldham et al., 2018). Nonetheless, integrating all the possible pathways to understand delirium is cumbersome in the ED setting, where the pace of the disposition of the patients does not always follow the pace of the diagnostic or causation process. Overall, there is the problem of delirium being indiscriminately both the clinical syndrome and a diagnosable disorder, classically the dichotomy between encephalopathy (more akin to neurologists and general internists) and delirium, where the latter is more attainable for psychiatrists and intensivists. So, this has implications on what should be defined as risk and vulnerability factors, particularly in the ED setting where the clinical relevance may be hindered by time and disposition constraints. The more logical convergence to integrate what is amenable to be operationalized in the ED is the identification of upstream of precipitants once delirium as a phenotype is evidenced.

Thus, there is a need to: (i) define the concept of procognitive factors and how they do relate with cognition; (ii) frame the precipitants or biological insults that lead to delirium by way of neurophysiological disruption; and (iii) define the neurophysiological disruption as a way to elucidate key relationships between neurophysiology and both its upstream precipitants and resultant phenotype (Oldham et al., 2018, 2022; Oldham & Holloway, 2020).

2.1.2. Prevalence and etiologic subtypes

Only after consensus on definitions, or on diagnostic criteria, can we have an epidemiological perspective of delirium across different settings. Much of this work deals with the conundrum of finding a common language between clinicians and researchers on what delirium means. Parallel to this, the estimates of delirium vary considerably by patient group and setting (Wilson et al., 2020), and there is a lack of robust epidemiological studies. However, the incidence and prevalence of delirium in hospitals appears to be stable, though publication bias may mask true changes (Gibb et al., 2020). Surprisingly, the reported variation in delirium in the ED has a narrower range than, for example, older longer-term care residents (LCT), as framing along both extremes of acuity on the spectrum of care: 8 to 17% in the ED (Kennedy et al., 2020; S. Lee et al., 2021) compared with a reported prevalence of 15 to 70% in

LCT (Pérez-Ros & Martínez-Arnau, 2019). However, there is evidence that the prevalence of delirium varies in geriatric patients in different EDs (Chen et al., 2022). Some data also points for regional differences in delirium prevalence, which may be due to different socioeconomic status (Ohl et al., 2019; Chen et al., 2022).

The classic psychomotor subtypes, namely hypoactive and hyperactive, may have an influence, as hypoactive delirium can be more difficult to recognize than hyperactive delirium, and it is associated with worse outcomes (Hosker & Ward, 2017). In addition, hypoactive delirium is the most common in the emergency setting (Han et al., 2009). The chief difficulty with operationalizing delirium, again, is that the boundaries of the main constructs are not clearly defined (D. H. J. Davis et al., 2013).

Despite these limitations, the aim is to operationalize criteria so that case-ascertainment can be achieved in a consistent manner (D. H. J. Davis et al., 2013). For example, delirium severity and psychomotor features provide important prognostic information and should be integrated into the assessment of delirium (Yang et al., 2009). Hence, we may group/classify deliria in the ED as both comprising psychomotor features and of etiological factors in order to have a workable plan of action and a practical framework (Table 3; Table 4). Important to note is the concept of subsyndromal delirium, where the phenotype presented does not fulfill the complete criteria for delirium diagnosis, without specifying which symptoms are present (Bowman et al., 2021). There is a rationale behind the classification on motoric subtypes, as these may point to specific neural circuits (Bowman et al., 2021). Moreover, data from a prospective study of 1,613 patients found in-hospital mortality to be the highest for patients with hypoactive or mixed subtypes (van den Boogaard et al., 2012).

Most studies on subtypes of delirium were done in the ICU and have focused on motoric subtypes. However, delirium can also be examined according to clinical phenotypes in an effort to identify clinical risk factors and potential underlying causes of delirium that may be useful to guide therapy or predict outcomes (Hughes et al., 2020). More so, emerging evidence has begun to suggest that, although initially useful in research and practice, current disease concepts do not sufficiently capture the full complexity of critical illness (Maslove et al., 2022). Take the example of the ED, as is the ICU setting, where conditions like sepsis, ARDS, acute kidney injury, delirium, and even chronic critical illness, are characterized not by any biopsy feature, genetic mutation, microbial culture or serologic test but, rather, by collections of signs and symptoms that together paint the picture of a clinically recognizable entity (Maslove et al., 2022). This syndromical approach has not been thoroughly tested for delirium, including in the ED. However, research has shown that multiple factors interact and work together, for

instance in older/elderly patients, to disrupt large-scale neuronal networks in the brain and manifest as delirium (Lagarto & Cerejeira, 2016). Hereafter, the evolution for the integration as delirium disorder offers a means of unifying the models of delirium and acute encephalopathy. It encompasses the presenting symptoms ("delirium"), pathophysiological complexity, and underlying causes, and encourages the field to move beyond subtyping delirium based solely on the level of motoric activity (Oldham et al., 2022). Therefore, aware of the inherent limitation in the syndrome-based classification of the current criteria based on clinical findings, here we try to underpin the underlying biological processes that give rise to them (Oldham et al., 2018; Maldonado, 2018; Maslove et al., 2022; Oldham, 2022).

In Table 3 and Table 4 we classify both in motoric activity and clinical clusters, giving some practical information and context regarding neurophisiolgy and interventions within the ED.

Table 3 Etiologic subtypes based on psychomotor features (Adapted from: Oldham et al., 2018; Pérez-Ros & Martínez-Arnau, 2019; Bowman et al., 2021)

Subtype	**Subsyndromal**	**Hyperactive**	**Excited Type**	**Hypoactive**	**Catatonic Type**	**Mixed**
Clinical features	Incomplete presentation of the syndrome (Cole 2003); it describes symptoms that do not fulfill complete criteria for delirium diagnosis, without specifying which symptoms are present (Bowman et al., 2021)	Range from simple restlessness to constant movement and agitation Memory impairment (for instance, patients can have an inability to remember recent events or difficulty in remembering instructions) Disorientation (first in reference to time and then to place) Incoherent speech and rambling or irrelevant conversation, or unclear or illogical flow of ideas Illusions and misinterpretations, which arise from a false impression of an actual stimulus. Visual hallucinations are the most frequent, often occurring at night Excessive daytime sleepiness with insomnia at night, fragmentation, and reduction of sleep or complete sleep-cycle reversal	Represents an extreme form of hyperactive delirium (Oldham et al., 2018)	Slowing or lack of Movement, paucity of speech with or without prompting, and unresponsiveness Memory impairment Disorientation (first in reference to time and then to place) Lethargy, drowsiness, apathy Confusion Sometimes patients can also appear to be sedated	Represents an extreme form of hypoactive delirium (Oldham et al., 2018)	Manifest both hypoactive and hyperactive elements

Table 3. *Cont*

Subtype	Subsyndromal	Hyperactive	Excited Type	Hypoactive	Catatonic Type	Mixed
Practical tips and likely diagnosis	Patients display one or more symptoms without having the full syndrome of delirium; may precede or follow an episode of full-blown delirium or may never progress to full-blown delirium (Cole 2003); may be considered as part of a spectrum of delirium severity, when measuring the core diagnostic features (Bowman et al., 2021)	The patient may speak louder, faster, and more often. Their actions are faster and less controlled, with increased activity and wandering. There is increased awareness, alertness, restlessness, fear, and higher likelihood of hallucinations and euphoria than in hypoactive delirium	Is associated with the use of sympathomimetic drug abuse (eg, psychostimulants, designer drugs [like the synthetic cathinone 3,4-methylenedioxymethamphetamine], or "bath salts"), which may lead to a hypermetabolic syndrome and potentially death, if not promptly recognized and treated (Oldham et al., 2018)	There are 2 main differential diagnoses for hypoactive delirium: a patient with severe depression can be apathetic and seem to be withdrawn when being addressed. However, a difference with hypoactive delirium is the absence of fluctuations throughout the day and of disturbance in consciousness. Another important differential diagnosis to consider is a preexisting dementia, which will have had a gradual onset. It is possible for a delirium to superimpose on dementia, but also in this combination, a sudden change in behavior and alertness should be noticed. Aripiprazole and methylphenidate showed promising results in the treatment of hypoactive delirium (Lodewijckx et al., 2021)	There is evidence that patients with catatonic delirium showed higher frequencies of viral and anti-NMDAR encephalitis, as compared to patients with delirium without catatonic syndrome. Brain tumors, subarachnoid hemorrhage, acute hydrocephalus, epilepsy, and ischaemic stroke were associated with delirium without catatonic signs.	Behavioral rating scales can be used to track the progress of the patient. RASS may be a useful scale best suited to the ED environment (Han et al., 2015)

Table 4 Symptom clusters and discret mechanistic subphenotypes incorporating the pathophysiology of delirium and integrating interventions (Adapted from: Oldham et al., 2018, 2021, 2022)

ED Clusters	Delirium Precipitant	Delirium Neurophisiology	Intervention
Cardiovascular/Pulmonary	Cerebral hypoperfusion (heart attack or heart failure) or hypoxia (COPD or pulmonary embolism) Pneumonia	Oxidative stress Direct damage changes in the cerebral parenchyma, in an acute or chronic form, causing organ dysfunction, by (i) cerebral hypo-perfusion, with insufficient supply of blood flow, insufficient oxygenation and supply of glucose and other nutrients and important substances for the proper functioning of the brain); and (ii) arteriosclerosis, with destruction of the arterial vessels, which contributes to the above-described processes, as well as providing small insults that accumulate with age (such as micro-haemorrhages)	Restore circulation to hypoperfused, ischemic, or hypoxic tissues Antibiotics
Genitourinary/infection/dehydration/renal damage	Peripheral infection (e.g., urinary tract infection) Sepsis-associated encephalopathy	Neuroinflammation	Antibiotics
	Electrolyte disturbances (e.g., hyponatremic) Encephalopathy, hypercalcemia induced psychosis	Neurotransmitter dysfunction	Careful correction of disturbances
	Uremic encephalopathy	Neuroinflammation Oxidative stress Glutamatergic overactivity (due to uremic toxins, especially nitric oxidase-inhibiting guanidine compounds)	Renal replacement
	Cystocerebral syndrome (i.e., encephalopathy due to urinary retention)	Dysautonomia (afferent β3-adrenergic activation due to bladder distention)	Bladder decompression

Table 4. *Cont.*

ED Clusters	Delirium Precipitant	Delirium Neurophisiology	Intervention
Hepatic/Gastrointestinal/Endocrine/metabolic	Hepatic encephalopathy	Glutamatergic overactivity (due to high ammonia)	Lactulose, rifaximin
		Cerebral edema related to elevated glutamine	Early evidence: probiotics, branched-chain amino acids, L-ornithine, L-aspartate, Flumazenil (benzodiazepine antagonist)
		Neuroinflammation	
	Fecal impaction	Dysautonomia (sympathetic and parasympathetic innervations involved)	Digital evacuation of the impacted fecal mass or the rectal administration of stool softening agents, usually enemas or suppositories
	Thyrotoxicosis	Neuroendocrine (HPA axis), neurotransmitter dysfunction	Intravenous fluid replacement, treatment of hyperthermia, thyreostatics, Beta-adrenergic blockade
	Hypothiroidism (*myxedema madness)*	Neuroendocrine (HPA axis), neurotransmitter dysfunction	Leovthyroxine
	Hyperglicemia	Cerebral metabolic insufficiency	Fluid replacement, Insulin
	Hypoglicemia		Glucose replacement

Table 4. *Cont.*

ED Clusters	Delirium Precipitant	Delirium Neurophisiology	Intervention
Central Nervous System	Paraictal encephalopathy	Network dysconnectivity	Antiepileptics for seizures, though their use for encephalopathy per se is untested
	Traumatic brain injury	Glutamatergic overactivity Oxidative stress Associated structural damage (DAI, focal ischemia, BBB breakdown)	Nonpharmacologic interventions: amantadine has been studied later in recovery, and neuroleptics in particular may hinder cognitive recovery
	Anti-NMDA receptor encephalitis	Glutamatergic overactivity Neuroinflammation	1st line: corticosteroids IVIG/plasmapheresis 2nd line: rituximab, cyclophosphamide, and less commonly the antimetabolites azathioprine, mycophenolate, methotrexate
	Malignant catatonia	GABA-ergic deficit Glutamatergic overactivity	Benzodiazepines and electroconvulsive therapy
		Dysautonomia (excess noradrenergic tone)	Early evidence:NMDA receptor antagonists, valproic acid, carbamazepine, thyroid (T3)supplementation

Table 4. *Cont.*

ED Clusters	Delirium Precipitant	Delirium Neurophisiology	Intervention
Surgical situations, which in themselves can induce either direct damage to the brain, or inflammatory responses (before, during and after the surgical act), *aberrant stress responses*	Postoperative state (non-cardiac surgery)	Neuroinflammation	Nonpharmacologic interventions alone
Major Toxidromes	Anticholinergic toxidrome	Cholinergic deficiency	Physostigmine (optional/potentially diagnostic)
	Corticosteroid intoxication	Neuroendocrine (HPA axis)	Limit corticosteroids as feasible; Antiglucocorticoids (e.g., ketoconazole or mifepristone)
	Benzodiazepine intoxication	GABA-ergic overactivity	Flumazenil (optional/potentially diagnostic)
	Alcohol withdrawal delirium	Glutamatergic overactivity	Benzodiazepine
		Dysautonomia (excess noradrenergic tone) Glutamatergic overactivity	Early evidence: valproic acid, carbamazepine Alpha-2 Adrenergic Receptor Agonists (e.g. Dexmedetomidine)
	Valproic acid (VPA)-associated hyperammonemic encephalopathy	VPA-induced carnitine deficiency →high ammonia → glutamate excess, cerebral edema related to elevated glutamine	Levocarnitine and discontinue valproic acid

Notes: BBB: blood-brain barrier; COPD: chronic obstructive pulmonary disease; DAI: diffuse axonal injury; GABA: gammaaminobutyric acid; HPA: hypothalamic-pituitary-adrenal; IVIG: intravenous immunoglobulin; NMDA: N-methyl-D-aspartate; VPA: valproic acid;

2.2. Overview of delirium pathophysiology

From Engel and Romano in the 1940s to Lipowski in the 1990s, the pathophysiology of delirium has brought about a thread of ideas that, altogether, postulate that the cerebral insufficiency leading to delirium likely involves one or more of the following pathophysiologic mechanisms: abnormal blood flow, abnormal energy metabolism, abnormal neurotransmission, and abnormal cellular maintenance processes (Williams, 2013).

Regardless of delirium subtype, the pathophysiology of delirium remains unclear, yet an understanding of this is essential for developing pathophysiological-targeted treatments essential for precision medicine (Oh et al., 2020). Much of the uncertainty probably yields from that distinct neurobiological mechanisms or combinations of them are involved in delirium pathogenesis (Wilson et al., 2020). Thus, although the precise pathophysiology of delirium remains speculative (Bellelli et al., 2021), there have been attempts to frame the neurobiology of delirium from a systems integration failure hypothesis (SIFH) (Maldonado, 2008). This hypothesis integrates precipitant factors, delirium substrates, and clinical factors, as a cause for acute brain failure leading to specific delirium phenotypes and its associated outcomes. From this perspective, delirium is highlighted from its complexity, even proposing a refined model of delirium disorder, composed of interactive elements, which both elucidates key relationships and clarifies delirium nomenclature (Oldham et al., 2018). However, the principal problem will always be to balance a pragmatic view, which fulfills the minimum for a clinical approach, and a deep understanding of the neurophysiological mechanisms, which would orient novel treatment targets. This is particularly relevant in the ED environment. Knowing the phenomenon of delirium by its 5 core domains, namely: 1) cognitive deficits, 2) attentional deficits, 3) dysregulation in circadian rhythm, 4) emotional dysregulation, and 5) alteration in psychomotor functioning, has been valuable in highlighting its importance for patient outcomes (Wilson et al., 2020). However, when trying to disentangle all the intricate mechanisms that lead to the common phenomenon, a causative approach, based on aetiological contributors (that is, the underlying acute pathophysiological disruption or precipitants leading to delirium) (Wilson et al., 2020; Oldham & Holloway, 2020), is more useful. Thus, we will follow from the perspective of the factors that influence the ageing brain, and promote vulnerability, to a discrimination of mechanistic factors that precipitate delirium. Essentially, it is sought to describe the varying degrees of specific physiological characteristics (i.e., substrates) and relate their load to acute precipitant factors (Maldonado, 2018). It is not an easy task.

2.2.1. Degenerating brain vulnerability

The neuronal ageing hypothesis is based on the well-stated model of changes that the brain undergoes as people age. The European Delirium Association and the American Delirium Society state that delirium is unquestionably a marker for vulnerability (EDA/ADS 2014). A crude view at the numbers, in an epidemiological frame, tells the story: the risk of delirium increases steadily in hospitalized subjects from 3% in the young to 14% and 36% in older (aged 64–74 years) and elder individuals (Pandharipande et al., 2014), giving a rough grow of about 2% per year after the age of 65 (Pendlebury et al., 2015).

Age alone correlates linearly with delirium risk in any hospital setting and, within the mechanisms precipitating delirium, there are several factors that explain an age-specific vulnerability, which are highlighted in Table 5 (Maldonado, 2018). Although the relationship with age is not necessarily straightforward, as there is an amount of data that points to a U-shaped distribution of brain vulnerability to delirium in relation to age, it does, nonetheless, also reflect the availability of functional reserve and supports the relevance of its pathogenic role in lifetime delirium (Bugiani, 2021). There is also evidence that a cognitive reserve theory is consistent with the theory of plasticity in cognitive ageing neuroplasticity (Cizginer et al., 2017; Shafi et al., 2017).

Table 5 Potential mechanisms associated with the increased risk of delirium in the elderly. (Adapted from: Maldonado, 2018)

- Neuronal loss (particularly in locus coeruleus and substantia nigra
- Changes in various neurotransmitter systems
- Age-related decline in white matter integrity, observed as increases in water diffusion and volume of hyperintense white matter lesions, intergyral spans, and reduction in fractional anisotropy of water diffusion, correlated with a decline in the global and regional cerebral glucose uptake
- Age-related decline in regional cerebral blood flow, particularly in the anterior cingulate gyrus, bilateral basal ganglia, left prefrontal, left lateral frontal, and left superior temporal and insular cortex, as measured by single-photon emission tomography
- Age-related changes in cerebral blood flow, likely associated with brain microvascular pathologies
    - rarefaction of the microvasculature in some regions of the brain
    - decreased vascular density
    - damaged microvessels, with associated microinfarcts and microhemorrhages, likely due to peripheral arterial aging leading to stiffening and dilation of the proximal aorta with transmission of flow pulsations downstream into the brain
    - decline in cerebrovascular angiogenesis
    - impaired cerebral blood flow due to tortuous arterioles and deposition of excessive collagen in veins and venules
- Age-related decline in cerebral metabolic rate of oxygen more markedly in bilateral putamen, left supratemporal, left infrafrontal, and left parietal cortices
- Decreased oxygen supply (eg, hypoxia) leading to a decrease in redox activity, resulting in decreased acetylcholine (ACh) production (oxidative stress)
- Decreased cerebral oxidative metabolism

Table 5. *Cont.*

• Age-related changes in brain neurochemical activity:
  o There is a significant increase in soluble hexokinase activity with age, due to an increased release of mitochondrial-bound hexokinase
  o There is a negative correlation of the activity of fructose-6-phosphate kinase with age, particularly in the brain cortex and putamen
  o There is a significant decline of carbonic anhydrase (important in the regulation of the pO2/pCO2 ratio in the brain tissue) with increasing age. Thus, pCO2-dependent regulation of tissue pH, ionic transport processes, and cerebral blood flow regulation have the tendency to become more and more unstable
• There is a progressive, age-dependent decline in cyclic adenosine monophosphate–dependent activity, most significantly in the brain cortex and thalamus, followed by the hippocampus, amygdala, and globus pallidus

• Age-related cerebral changes in stress-regulating neurotransmitter and intracellular signal transduction systems (neurotransmitter hypothesis)

• Decreased ACh levels in plasma and cerebrospinal fluid, which may lead to:
  o Decreased volume of ACh-producing cells associated with normal aging (neurotransmitter)
  o Decreased ACh synthesis associated with aging
• Increase in baseline levels of circulating inflammatory mediators including cytokines and acute phase proteins (neuroinflammation)

We will next explore different neurophysiologic mechanisms.

2.2.1.1. Disrupted cerebral metabolism

In humans as much as one-fifth of the total energy is consumed by the brain, a remarkable amount for an organ that accounts for only 2% of the total body mass (Rolfe & Brown, 1997). There is a strong appeal to link brain metabolism to the concept of cerebral insufficiency, as we do with the heart or kidney in syndromes of cardiac failure and kidney failure (Slee, 2012; Bertero & Maack, 2018). In fact, the hypothesis of "cerebral metabolic insufficiency" is a long standing one since the seminal work of Engels in 1959 (Engel & Romano, 2004). Thus, when we address brain metabolism, we are mainly concerned with blood flow and oxygenation, supply and use of energy substrate, and in this frame,

delirium results from the failure to meet the energy requirements of the brain. Any state that may contribute to decreased oxygenation (e.g., pulmonary or cardiac failure, hypotension, anemia, hypoperfusion, intraoperative complications, hypoxia, anoxia, carbon monoxide poisoning, shock) is a known risk factor for the development of delirium (Maldonado, 2017).

Overall, even with its extraordinary ability to function under many conditions, the brain cannot produce enough energy to support its normal activities when either oxygen or glucose supply is inadequate (Dienel, 2019). However, as straightforward as it may seem, there are still many gaps in the demonstration of such a link between brain bionergetics and delirium.

2.2.1.2. Cerebral Glucose Metabolism

The evidence that glucose is the obligatory fuel for the adult brain derives from insulin-induced hypoglycemia (Dienel, 2019). Neurons and astrocytes both require a massive amount of glucose, supplied by the microvasculature, to generate adenosine triphosphate (ATP) by glycolysis (Wilson et al., 2020). Glucose is not only used for ATP generation, but it is also the precursor for many compounds synthesized within the brain, including neurotransmitters and neuromodulators (Dienel, 2019). Evidence from Tomography (FDG-PET) imaging in mice have shown that glucose uptake is substantially reduced with sepsis (Semmler et al., 2008), and overall glucose metabolism is impaired during delirium in humans (Haggstrom et al., 2017). The influence of hypoglycemia on human physiology and brain function is well known and described: reduction of human arterial plasma glucose level from the normal range of 72–108 mgl/dl to 54 mg/dl causes endocrine responses and symptoms of hypoglycemia (e.g., anxiety, palpitations, hunger, tremor, sweaty, dizziness, and weakness), a further decrease to 47 mg/dl causes cognitive dysfunction (difficulty speaking and thinking and blurred vision), 30 mg/dl is associated with mild confusion and delirium, 20 mg/l leads to cognitive failure, stupor, and seizures, and 10 mg/dl causes coma and, ultimately, death (Dienel, 2014, 2019). On a clinical ground, the effect of hypoglycemia is well documented in critical ill patients, and it is strongly associated with increased risk of mortality (Van den Berghe et al., 2006; Krinsley et al., 2011). The relation between delirium and hypoglycemia seems more pronounced in diabetic patients (van Keulen et al., 2018; Zhao et al., 2022).

2.2.1.3. Cerebral oxygen metabolism and cerebral hemodynamics

Within the framing of brain bioenergetics, poor cerebral perfusion may contribute to delirium. Behind such is the concept of cerebral autoregulation (CA), a physiologic process which consists in the innate ability of the cerebral vessels to maintain a relatively constant cerebral blood flow (CBF) over a wide range of systemic arterial pressures (Lassen, 1941; Sainbhi, 2022). Reliable cerebral perfusion measurements during critical illness have only recently become available (Wood et al., 2017; Sainbhi, 2022). Related with the CBF, the evidence that oxygen deprivation leads to delirium in humans is demonstrated by near infrared spectroscopy (NIRS), a noninvasive technique to measure regional oxygenation saturation (rSO2) in tissue beds beneath the sensors, and not dependent on pulsatile flow (Bendahan et al., 2019). Low rSO2, as measured by NIRS, may be associated with delirium in critically ill patients (Bendahan et al., 2019). It is very difficult to disentangle the roles of CBF and oxygen metabolism. Cerebral oxygen metabolism and cerebral hemodynamic disorders have a key part in developing Sepsis Associated Delirium (SAD) (Burkhart et al., 2010; Feng et al., 2021). Microcirculatory dysfunction and dissociation between cerebral cells' needs and perfusion at several cerebral areas was found in an experimental sepsis model (Rosengarten et al., 2009; Mihaylova et al., 2012). However, there are conflicting results in humans, and microcirculatory dysfunction is not widely assessed, as, to date, no widely applicable method exists to evaluate cerebral perfusion with wide acceptance (Sharshar et al., 2010; Pierrakos et al., 2013). Notwithstanding, non-invasive methods, like Transcranial doppler (TCD) assessment of cerebral perfusion, suggest that cerebral vascular constriction is detectable by TCD in the early stage of sepsis, which is consistent with experimental data documenting impaired cerebral microcirculation at the onset of septic shock, as well as in septic patients, with delirium (Szatmári et al., 2010; Taccone et al., 2010; Pierrakos et al., 2013). Also, in other studies, the use of TCD allowed the finding of disturbed cerebral autoregulation in patients with SAD, but not in patients with "plain" sepsis (Pfister et al., 2008). According to it, indices of dynamic autoregulation assessed using NIRS and TCD agree in adults with sepsis (Steiner et al., 2009). This suggests that CA is possibly intact in patients with sepsis but disturbed with more severe disease or in complications manifesting as septic shock or sepsis-associated delirium (Burkhart et al., 2010).

Outside the ED setting, surgery/the operating room has been a "laboratory" to study the specific relations between perioperative blood pressure (BP) variability, hypertension (HTN) and hypotension (HPT), which have all been associated with hemodynamic instability and poor clinical outcomes (Lizano-Díez et al., 2022). Many studies, both in cardiac and non-cardiac surgery, used delirium as a surrogate

endpoint in the early post-operative period (Hirsch et al., 2015; Hori et al., 2016; Lizano-Díez et al., 2022). Interestingly, fluctuations in BP during surgery, besides absolute or relative values of hypotension, were associated with early postoperative delirium (Hirsch et al., 2015). However, it seems clear that there is a potential benefit from improved management of BP in terms of short and long-term effects of surgical procedures in patient outcomes (Lizano-Díez et al., 2022). Translating this knowledge to other settings, like the ED, could be cumbersome, but there is a potential for TCD, and Point-of-Care Ultrasonography in general, to better evaluate the hemodynamic status of any patient non-invasively and at the bedside (Ali et al., 2011a; Caplan et al., 2014). Particularly in the ED, the role of chronic hypoperfusion, as in cerebrovascular disease or heart failure, represents vulnerability to delirium (Iadecola, 2013; Oldham et al., 2018).

2.2.1.4. Neuroinflammation and oxidative stress

Systemic inflammation is a prominent feature of numerous medical and surgical conditions associated with delirium (Cerejeira et al., 2010). The precise mechanisms by which it disrupts brain function is not clearly understood and most of the discussion here relates to animal model studies (Wilson et al., 2020). It is now well established that CNS resident cells react to the presence of peripheral immune signals, leading to production of cytokines, and other mediators, in the brain, as well as cell proliferation, and activation of hypothalamus–pituitary–adrenal axis, through a complex system of interactions (Cerejeira et al., 2010). A further mechanism by which the brain can detect systemic inflammation is through afferent vagal fibers ending in the nucleus tractus solitarius, which senses visceral inflammation through its axonal cytokine receptors (Burkhart et al., 2010).

Although many of these findings require validation in patients, it is clear that inflammation induces pathways that are activated during delirium in many clinical settings (MacLullich et al., 2008; Wilson et al., 2020). In critically ill patients, there is evidence that plasma biomarkers of inflammation, coagulation, endothelial activation, and Blood Brain Barrier (BBB) injury, is associated with delirium (Girard et al., 2012; Hughes et al., 2016; McNeil et al., 2019).

Another mechanism by which the brain is affected in sepsis is in the generation of oxidative stress and formation of Reactive Oxygen Species (ROS) by activated leukocytes, compromising cell function, and endothelial activation, and resulting in disruption of the blood-brain-barrier (Burkhart et al., 2010). The interplay between oxidative stress and hemodynamics is amplified where reduction or no change in CBF has been reported in endotoxin animal models (Maekawa et al., 1991), thus aggravating the cerebral

hypoperfusion seen in sepsis or even acting as a direct insult without a change in CBF. Evidence from cardiothoracic surgery patients points to the magnitude of intraoperative hyperoxic cerebral reperfusion being independently associated with delirium following cardiac surgery and increased oxidative injury may contribute to this association (Lopez Marcos G., Iv & Sc, 2017).

However, the complex milieu of the ED requires challenging methodologies to isolate the role of inflammation. Few studies have addressed the role of plasma biomarkers of inflammation with ED delirium duration in older ED patients admitted to the hospital. However, there is data that points to systemic inflammation and endothelial dysfunction being associated with delirium pathogenesis, though this association may be modified by baseline cognition (McNeil et al., 2019). There is, also, strong evidence of a relation between the cholinergic system and innate immune system over the cholinergic inflammatory pathway (Tracey, 2009; Isik & Grossberg, 2018). This interplay could offer new pathways for treatment of delirium, namely by the regulation of extreme stress response and neuroinflammatory pathways (Cerejeira et al., 2010; Cerejeira & Mukaetova-Ladinska, 2011; Isik & Grossberg, 2018). Additionally, nutritional and hydration status may influence metabolic disruption and energy deficiency leading to oxidative stress and neurotransmitter dysfunction (Riebl & Davy, 2013; Sanford & Flaherty, 2014).

2.2.1.5. Drugs and neurotransmitter dysregulation

Drugs have been associated with the development of delirium in the geriatric population and are considered a major, and potentially reversible, cause (Alagiakrishnan & Wiens, 2004; Clegg & Young, 2011a; Nguyen et al., 2018). Scales such as the Delirium Drug Scale, correlate with the incidence of Delirium at the time of admission in the ED (Nguyen et al., 2018).

However, the scrutiny of current drug use in a patient admitted to the ED is a cumbersome task. Since 1991, Beers criteria have been adopted regarding the drug's potential for adverse events (Beers et al., 1991; Steinman et al., 2017). The practical approach from applying the Beers criteria has been updated in 2019 and special guidance is given for drugs that have deliriogenic potential (Fick et al., 2019). Interestingly, the update highlights the growing evidence base for specific nonpharmacological approaches with a person-centered approach to care, with the area of care for persons with dementia and delirium being put forward as an example. There is a huge gap between studies in animals and the concept of "chemical insults" to the brain in humans and, therefore, inferences about a possible neurochemical basis of delirium is still common place. Trying to elucidate how experimentally disrupting

function in multiple neurotransmitter systems in animals can produce some features of delirium; however, trying to infer these different drug manipulations in humans may represent distinct neurochemical routes to delirium (Wilson et al., 2020). There is, nonetheless, an intricate relationship between medical conditions and theorized neurochemical mechanisms, and the most commonly described changes associated with the development of delirium include deficiencies in acetylcholine (ACH) and/or melatonin (MEL) availability, excess in dopamine (DA), norepinephrine (NE), and/or glutamate (GLU) release, and variable alterations (e.g., either a decreased or increased activity, depending on delirium presentation and cause) in 5-hydroxytryptamine or serotonin (5HT), histamine (His), and/or gamma-amino butyric acid (GABA) (Maldonado, 2017). Thus, although the pathophysiology of delirium is complex and incompletely understood, multiple neurotransmitter pathways are implicated, particularly cholinergic and dopaminergic pathways (Clegg & Young, 2011a).

Regarding the pathophysiology of neurotransmitter dysregulation and the influence of drugs on causing delirium, there is a consensus on specific drugs, corresponding mainly to three main groups: GABAergic sedatives, anticholinergic drugs and antihistamine drugs. Therefore, opioids, benzodiazepines, dihydropyridines and antihistamines appear to be associated with increased risk of delirium (Clegg & Young, 2011a). GABAergic sedatives, as represented by benzodiazepines, produce acute cognitive impairment and that increased GABAergic tone in the corticothalamic network is a major driver of unconscious brain states and is the basis of a hypothetical model of delirium pathogenesis (Sanders, 2011). The theory predicts that an acute upregulation of inhibitory tone within the brain acts to further disrupt network connectivity in vulnerable patients (predisposed by reduced baseline connectivity) precipitating delirium (Sanders, 2011). It is well known that in patients with hepatic encephalopathy increased inhibitory GABA levels also are observed. An increase in ammonia levels occurs in these patients, which causes an increase in the amino acids glutamate and glutamine, which are precursors to GABA. Decreases in CNS GABA levels are observed in patients with delirium resulting from benzodiazepine and alcohol withdrawal.

The link between acetylcholine and delirium is old and comes from studies both in humans and in animal models (White, 2002). Beyond the brain vulnerability from a variety of insults, the central cholinergic deficiency is often presumed to be the major pathogenic mechanism for delirium (Lipowski, 1990; White, 2002). There is even evidence of a role of acetylcholine in control of brain inflammation: microglia express nicotinic receptors and activation of these cholinergic receptors attenuates the pro-inflammatory response in vitro (Van Gool et al., 2010). Low levels of preoperative plasma cholinesterase

activity have been shown as a risk marker of postoperative delirium in elderly patients (Cerejeira et al., 2011), which has been associated with elevated proinflammatory markers in the circulation during acute illness (Abou-Hatab et al., 1999; Hubbard et al., 2008), and following inoculation to peripheral lipopolysaccharide, suggesting a significant immune–cholinergic interaction (Cohen et al., 2003; Ofek et al., 2007). Anticholinergic syndrome has been widely documented in the literature as "red as a beet, dry as a bone, blind as a bat, mad as a hatter, hot as a hare, full as a flask" (Ramjan et al., 2007), so the clinical support for the cholinergic hypothesis is strong.

Elevation of dopamine has been associated with the development of delirium (Ali et al., 2011b). In fact, anti- psychotic drugs, which largely function by blocking D2 dopamine receptors, have long been used in delirium treatment (Wilson et al., 2020). However, the current evidence does not support routine use of haloperidol, or second-generation antipsychotics, to treat or prevent delirium in adult inpatients (Nikooie et al., 2019; Ohl et al., 2019; Andersen-Ranberg et al., 2022). Dopaminergic status may affect the psychomotor state during delirium but is unlikely to have a mechanistic role in delirium at the syndromic level. So, a hyper-dopaminergic theory of delirium lacks robust basic and clinical data (Wilson et al., 2020). Future research should focus on defining patient subgroups and settings in which the benefits of antipsychotics outweigh harms, such as short-term use for behavioral control (E. Marcantonio, 2019).

First generation H1 antihistamines significantly increased daytime sleepiness and nocturnal sleep quality (Chazot et al., 2019) and were noted historically to be sedatives even before they were defined as a neurotransmitter (Monnier et al., 1967). Histamine is, arguably, the most pleiotropic neurotransmitter in the human brain, and while permeable H1 and H2 histamine receptor antagonists have pro-delirium potential, antagonizing H3 and H4 histamine receptors promisingly appear to show an anti-delirogeneous strategy (Chazot et al., 2019). Histamine driven H1 and H2 receptor-mediated actions are mostly excitatory, while H3 receptors act as inhibitory auto and heteroreceptors (Panula et al., 2015). Interestingly, the H4 receptor has a link with neuroinflammation, indirectly through modulating activated microglia (Zhou et al., 2019). Caution is required when prescribing dihydropyridines and antihistamine H1 antagonists while there is uncertainty regarding the risk of delirium associated with H2 antagonists (Clegg & Young, 2011b).

2.2.1.6. Neuroanatomical substrates and failure of network connectivity

Researchers in cognitive neuroscience, who first began to use neuroimaging to study human brain function, unexpectedly found that large, distributed regions of the association cortex show reduced activity when participants perform active attention demanding tasks, relative to their activity levels during passive conditions (Buckner & DiNicola, 2019). Further research in delirious patients with functional Magnetic Resonance Imaging (fMRI) showed the loss of network integration and efficiency may reflect the underlying neural mechanism for the cognitive dysfunction during the syndrome (van Montfort et al., 2018). During delirium, the reversal of the relationship between areas of the executive network and areas which are part of the default mode network (DMN), is a contributor for the clinical features such as inadequate shifting and focusing of attention (Wilson, 2019). DMN, thus, plays a more important role in response to acute neurophysiologic stress (Choi et al., 2012) and systematically identifying the brain features related to brain connectivity and plasticity has significant implications across a broad range of neuropsychiatric and cognitive diseases (Shafi et al., 2017). The results of a functional imaging study of patients with delirium superimposed on dementia suggest that changes occur in network connectivity, particularly the posterior cingulate cortex, during an episode of delirium (Fong & Inouye, 2022).

2.2.1.7. Other mechanisms

When there is no neuroanatomical/neurophysiological basis to develop delirium, people who "do not fit" within any of the theories will be left in a gray zone of predisposition, and this will be more frequent in patients in the ED. Thus, there are "Do Not Miss" conditions to consider in delirium, which in the ED resume all the above referred, considering so a practical basis for action: hypoxia/ hypercarbia/ respiratory failure, hypoglycemia, stroke, acute myocardial infarction, epidural/ subdural hematoma, herpes encephalitis, alcool/ drug intoxication or withdrawal, toxic exposures (e.g., carbon monoxide), myxedema. However, trying to convert a "gray zone" into something clear to act on could be very difficult. One approach could be the identification of clusters (Lagarto & Cerejeira, 2016), although the approach has not been studied in the ED specifically. Sleep and circadian rhythm integrity, which influences arousal, attention, memory, and state stability (Goel et al., 2013), is an apparent avenue. Disturbances of the circadian sleep–wake cycle represent one of the core features of delirium, leading to the hypothesis that the neurotransmitter melatonin and changes in its metabolism may be involved in the pathogenesis of delirium. The administration of prolonged release melatonin at 2mg or 3–5mg immediate release before bedtime might prevent the incidence of delirium in at risk population, but

consensus has been uncertain and, thus, more studies are needed for recommendation into the clinical practice (Palagini et al., 2021). For instance, while a recent meta-analysis showed that early administration of melatonin may result in a decreased delirium prevalence in critically ill patients, the sensitivity analysis of high-quality studies did not support this finding (Yan et al., 2022).

Finally, several pre-cognitive factors add complexity for possible relations with delirium. The neuropsychological effects of sensory deprivation have been studied for more than half a century, yet it is unclear how disruption of sensory input may compromise cognition (Oldham et al., 2018). Physical activity level, mainly as advanced frailty and the degree of socialization both requires activation and coordination of complex neural networks, and as such, may contribute to delirium burden. These factors, in a busy and crowded ED, may work as precipitant (external) factors not accountable by any systematic means owing to the differences between different EDs. For example, in an observational study of 254 acutely admitted geriatric patients an association between nighttime investigations and incident delirium was found. Therefore, the hospital environment in itself might be a target for delirium prevention along with any other nonpharmacological delirium intervention program(s) (Evensen et al., 2018).

2.3. The problem of "Gold Standard" for delirium

There are a lot of problems in every validation study, but one of the main biases is the lack of a proper gold standard when trying to apply a new clinical measure scale (Regier et al., 2013). Validity of a test or set of criteria involves accuracy, determined in part through sensitivity and specificity, and usually measured against a "gold standard" that is considered valid (Sepulveda et al., 2016). Currently, there is no gold standard, or reliable biomarker (e.g., MRI or electroencephalogram correlates), for delirium diagnosis (Maybrier et al., 2018). A reliable yet-to-be-determined biological marker, perhaps electroencephalography or fMRI, would be an important addition to phenotype criteria validity assessment (Sepulveda et al., 2016). Thus, for now, a thorough clinical evaluation is considered the gold standard for diagnosis of delirium (Thom et al., 2019).

Most studies regarding the recognition of delirium come from the Intensive Care Units (ICU). The under-recognition of delirium in the ED is probably more accentuated than in the ICU, and it is a common rule that emergency nurses do not routinely evaluate ED patients for delirium, thus missing almost 70% of the cases (Barron & Holmes, 2013; Boucher et al., 2019; el Hussein et al., 2021). Owing to no gold

standard, and imperfect reference standards for delirium, some authors propose combining two different delirium assessment tools in the same patient within 6-hours (Moss et al., 2022).

3. The Problem of Defining Delirium in the Emergency Department

3.1. Framework of the ED

3.1.1. Structuring and functioning of the Portuguese ED

Modern EDs are at the core of every health system, where they are the "safety net of the safety net" (*2013 RAND Annual Report. Santa Monica*, 2014; Morganti et al., 2013; Selby et al., 2018). Their primary role is to provide high-quality care to patients, regardless of when they need medical help or what they present with (Graham, 2015). Modern EDs are the most central places in any Health System (HS), even considering HS according to differences in financial support, burden of unnecessary visits or other bench-works of performance. Behind the actual role of the EDs in any HS, there is an increasing capacity of its players in performing tasks which were, until recently, exclusive of some services (e.g., Intensive Care (IC)). Yet EDs have a unique environment, which is highlighted by the American College of Emergency Physicians in their Primer on Research stated in 2012, and applicable to the Portuguese setting, owing to the universal principles which are behind the very fundamental principles of medical care. Here we point to some specificities of the EDs that run universally whatever the HS where the ED is integrated:

- EDs offers both immediacy of care and universality of service;
- EDs are multidisciplinary and multiprofessional, encompassing and interacting with all medical specialties;
- EDs are literally the front door for the sickest and worst injured;
- EDs cover all patient populations, traverse all geographies, and interact with every culture, race, creed, and socioeconomic class.

Contrasting with its universal character, and the noble mission of privilege of care of the sickest and worst injured, EDs are confronted with huge problems worldwide, leading to serious dysfunctions, mostly related to crowding. In this respect, a growing body of evidence documents the adverse effects of ED crowding on clinically important outcomes, owing in great part to longer waiting times for first medical observation, with delays in admission, higher risk of infectious disease transmission, higher mortality among many other bad outcomes (Bernstein & Asplin, 2006; Machado et al., 2018). In fact, problems of the EDs, as we know them, date back to the sixties, where in the USA, for example, the

increased use was already taunted as the leading problem of EDs, which created pressures on the hospital and medical staff to provide a more adequate service ("The Emergency Department Problem," 1966). Decade after decade the problem has continued to grow, yet only in the later part of the 80s was it recognized and termed as "crowding" (Dickinson, 1989). Crowding in the ED is a problem worldwide, and there is strong evidence that one of the main reasons is a surplus of patients compared to physicians and beds (Trivedy, 2020). Central to it, critical crowding, and heavy emergency resource demand, hampers the delivery of high-quality medical care and compromises patient safety ("Definition of Boarded Patient," 2019).

Portugal is no exception. In fact, it has rates of visits to EDs considerably higher than other OECD country (OECD average 30.8 visits / 100 inhabitants, compared with an average of 70.2 visits / inhabitants in Portugal) (Alves Da Rocha, 2020). This pattern has remained fairly constant over the years (Health System review 2018). Additionally, the Portuguese central administration for health report states that 8.6% of the users are considered frequent users (4 or more visits in a year), and those 8.6% represent 27.9% of the ED visits (Health System review 2018). Furthermore, the demand for emergency care in Portugal increased by 5.2% between 2013 and 2019, reaching a peak of 6.4 million episodes, increasing the pressure on this type of services and overcrowding hospital emergency departments (Alves Da Rocha, 2020).

The ED environment is, not surprisingly, highly pressurized, immediate, emotional, and, often, overburdened (Good & Driscoll, 2002). Consequently, explicit and contextual scenarios of EDs are not elicited in a clear way. At the national level there are several issues to be resolved. Action is needed on the solution to identify the priorities. Planning any ED action requires professionals trained on the delivery of the best measures to support primary care practices by performing complex diagnostic workups and handling overflow, after-hours, and weekend demand for care (*2013 RAND Annual Report. Santa Monica*, 2014) Thus, the demand in the attention of the emergency services has been growing progressively in the last years, and this increase is more noticeable in the population of older adults. The number of geriatric patients visiting the ED has outpaced the educational emphasis in training programs and clinical resources available in the EDs dedicated to care for this population (Magidson & Carpenter, 2021).

The implications in delirium care in the ED is, thus, surmount. Any delay in disposition worsens delirium, and most delirious patients benefit from admission to the hospital for further work-up and management of the precipitating insult (Eagles & Khoujah, 2021). However, for instance, lack of

implementation of geriatric policies in the ED undermines every effort for care in particular patients with cognitive problems, which in the majority affect the elderly population. So, the perspective here is to frame from a single level of action, namely delirium, the problems faced in an ED. From this perspective we move forward from the problem of delirium as a global problem to a framed problem in the ED.

3.1.2. Brief note on observational units within the ED

There has been a trend on the diversification and specification of observational units within the ED. Particularly, geriatric emergency units are advocated by some important leaders and scientific organizations (Carpenter et al., 2014; Southerland et al., 2020). For the general population, observation units have demonstrated cost savings by averting inpatient hospitalizations (Baugh et al., 2012; Hwang et al., 2013). Some studies have demonstrated that the readmission rate of geriatric patients is lower from dedicated units than from the standard of care of the ED (Bosetti et al., 2020). There are multiple options for transition of care from the ED, including telemedicine, inpatient, admit-to-home, placement in observation care, send home with home care, and so forth, transforming the current safety-net role of the ED to becoming a partner in care coordination (Hwang et al., 2013; M. Rosenberg & Rosenberg, 2016).

Nonetheless, although an increasing number of hospitals have created EDIMCUs, for example, there is little data in the literature regarding delirium and outcomes in EDs and IMCUs (Junker et al., 2002) compared to the information in more critically ill patients. In fact, with respect to delirium management, the few studies conducted in Europe included only 3% of the doctors working in high-dependency units (Mac Sweeney et al., 2010). This may be unrepresentative given the growing relevance of these units in emergency settings according to health policy reports (Wild & Narath, 2005).

3.2. Translating delirium research into action

3.2.1 Improving research in the ED, how do we get there?

Many obstacles hinder the efforts for doing research in the EDs. The problems concern chaos for being too busy, lack of training in research, lack of staff for doing research with few mentors/role models, and a lack of interest in general. Moreover, research within the EDs is daunted with problems of overcrowding, lack of training in research, and beyond that, lack of motivation of its players to improve new models (Chan et al., 2017; Morley et al., 2018). Considering the problems that EDs face, research

seems like the last problem, on a priority list, to be addressed. Consider problems like sepsis, for example. We know that sepsis needs a proper understanding and action, where evidence-based guidelines, published regularly, reflect best practices and recommendations for the treatment of sepsis and septic shock in adults and are revised regularly to account for new research (Lat et al., 2021). But even on topics so well entrusted in critical care management as sepsis is, when we must translate from evidence-based guidelines to practice, in a varied ED setting, we are still adapting aspects of identification, diagnosis, and disposition. These problems are the cornerstone of every action in the ED. However, and in this line, the ED holds opportunities not only for large quantitative research projects but, also, for qualitative studies, audit and service evaluation involving a massive spectrum of clinical presentations, (O'Brien, n.d.). Thus, while the basic science questions regarding, for instance, the best assay for determining pregnancy or detecting at-risk myocardium while stressed are of interest, a clinical scientist is most interested in the clinical questions that guide the practice of emergency medicine (*Doing Research in Emergency and Acute Care*, 2015). Much of the problem comes from the narrowing field that players in the ED have. Owing to the constraints above mentioned, there is a lack of flexibility on going around the main problems in every ED, irrespective of the HS, mainly in aspects of feasibility, acceptability, usability, and effectiveness. For this, new approaches are needed, from implementation science to human factor engineering (Carpenter & Pinnock, 2017)

In the particular case of delirium in the ED, and/or acute care units, much of the problem regarding its incidence and prevalence relates in great part to the unique environment: intense time demands on providers and high volume of patients. Together these aspects can both (i) render caring for older adults challenging and (ii) hinder the use and validation of screening tools. This occurs despite any positive impact that this latter work would in itself yield, including early identification of delirium and translation into appropriate treatment measures. Nonetheless, the horizon of delirium research has hugely increased over the last 20 years. Much progress has been made in understanding the epidemiology of delirium with implications in the understanding of the prevention, treatment and clinical effects (Wilson et al., 2020). However, there is a stalemate on priorities. In a crude summary of the actual scene, research into biomarkers for delirium has been limited, and no objective delirium test with acceptable diagnostic accuracy has been identified (Harwood 2018). A recent review highlights the need for increased research because delirium related mortality has not improved over the past 30 years, whereas outcomes of other diseases have (Aung Thein et al., 2020).

Some authors strongly indicate that a one-size-fits-all approach based on a unitary biological model of delirium has contributed to variance in delirium studies and prevents further advance in the field (Oldham et al., 2018; Wilson et al., 2020). The problem resides in what we take to the most inclusive category of analysis. Comparing historically with the Glasgow Coma Scale (Todd et al., 2017), the problem must be framed in a way that every player in ED should be aware of what delirium is. We have lines of action that are very straightforward to action in trauma and sepsis, and taking that for comparison we see that delirium is only a bystander. Delirious patients should be evaluated based on those lines of action common for other heterogeneous clinical groups: triage systems tend to frame every altered level of arousal as a defined pattern based on those lines. To put it simply, there is a large number of patients with altered levels of arousal that simply if they don't have a "box" in the triage system to be put on, they are alone in the system, based on other symptoms that probably will take them to an inappropriate flowchart of decision making. This problem not only takes the frailty patient from his track, but more fit patients could also have the same final postponed ending. Some advocate, as it has been said above, referring to Delirium disorder (Oldham et al., 2018), that allowing to 'lump' all together delirium subtypes in certain settings will increase the awareness of the syndrome (Wilson et al., 2020). But transdisciplinary stakeholders prioritize ED delirium prevention studies that are not reliant upon healthcare worker tasks instead of alternative research directions such as defining etiologic delirium phenotypes to target prevention or intervention strategies (Carpenter et al., 2020). So, active screening, prevention, and intervention for those who are at risk for delirium, and its associated complications, are the next steps needed to improve care for older adults under our care and beyond (S. Lee et al., 2021).

Significant variability exists in reference standard methods for delirium diagnosis in published research. Increasing standardization by documenting inter-rater reliability, using standardized cognitive and delirium detection tools, incorporating diagnostic expert consensus panels, and using all available information in patients declining or unable to participate with formal testing, may help advance delirium research by increasing consistency of case detection and improving generalizability of research results (Neufeld et al., 2014). There is increasing agreement among delirium researchers of the need to operationalize the definition of delirium and to implement protocols to mitigate delirium when possible (Khachaturian et al., 2020). This should involve explicit descriptions of the constructs and domains, along with the use of quantitative, objective instruments that are well validated using formal psychometric approaches (ie, reliability, validity, discriminatory power, and normative data). At the same time, these new approaches need to consider the challenges of delirium assessment in real-world

practice (Oh et al., 2020). The next wave of ED-based delirium research must take a more comprehensive approach, utilizing principles of implementation science to develop delirium monitoring processes that can be pragmatically implemented and sustained in diverse ED settings—large, small, rural, urban, community, and academic (Harwood & Teale, 2018; Oh et al., 2020). This research needs to consider what tools to use, who should be evaluated (and how frequently), and the clinical response to a positive diagnosis. Outcomes must include not only diagnostic accuracy, but process and patient-based outcomes. Such research is feasible by leveraging existing ED-based research networks, such as the Geriatrics Emergency Department Collaborative and the Geriatric Emergency Care Applied Research (GEAR) network (Carpenter et al., 2020).

Different researchers on delirium have identified in the last years key aspects to do a research agenda for the upcoming years. Shenvi (Shenvi et al., 2019) identified five questions, among fourteen, which were pointed by a group of experts in emergency medicine (EM), geriatric EM, and psychiatry, and with high consensus for their importance related to the care of older adults with agitation in the ED. These five questions are directly related to the identification of delirium in the ED and the proper disposition of delirious patients within the emergency system:

- What are the barriers to diagnosis of delirium in the ED, and how can they be overcome?
- Is ED length of stay an independent risk factor for the development of delirium?
- Does ED length of stay contribute to worse morbidity and mortality or adverse medical events in older adults with delirium?
- What are the most effective non-pharmacologic interventions in the ED to manage or prevent delirium?
- Does having an ED pharmacist involved in patient care help reduce rates of delirium in the ED?

The Network for Investigation of Delirium: Unifying Scientists (NIDUS) held a conference “Advancing Delirium Research: A Scientific Think Tank” in June 2019 (Oh et al., 2020). From there, a proposal of a roadmap for advancing delirium research highlighted the discussion and key priorities for the field of delirium, which spanned the areas of delirium definition and measurement, pathophysiology, and prevention and treatment (Oh et al., 2020). The domain of definition and measurement had a considerable attention from the panel of experts, and although not referring specifically to the emergency setting as the above questions highlighted by Shenvi et al, the topics addressed pointed in the same direction, as there were identified the following priority areas to advance the definition and measurement of delirium:

- Consensus on the definition of delirium;
- Development of a reference standard approach for the diagnosis of delirium;
- Use of uniform, standardized measurement tools for delirium case identification and severity rating across different care settings;
- Identification of etiologic subtypes of delirium;
- Development and application of a core outcomes set for clinical studies in delirium.

More research using the neuropsychological approach has enormous potential to improve and standardize delirium assessment methods of the individual features of delirium, such as inattention, and in developing more robust reference standards to enable greater comparability between studies (Tieges et al., 2018).

3.3. The problem of delirium in the ED

Multiple guidelines advocate for the evaluation of mental status in all older patients presenting to the ED to assess for the presence of delirium (Kilshaw, 2009; Cooke et al., 2012; M. S. Rosenberg et al., 2014; Yue et al., 2014; Eagles & Khoujah, 2021). The epidemiology of delirium is influenced by the rate of detections and the generalization from some cohorts to the whole reality of different kinds of EDs is difficult to ascertain. Despite progress in the understanding of its clinical presentation, analysis of its clinical epidemiology, presentation and consequence to the overall clinical outcome remains complex (Thomason et al., 2005; Siddiqi et al., 2006; Cole et al., 2009; Han, Wilson, et al., 2010; Mitasova et al., 2012). On presentation to the ED, delirium is present in 8–17% of all elderly people and 40% of nursing home residents (Inouye et al., 2014).

In fact, although studies have indicated that delirium is a predictor of a longer hospital stay (Thomason et al., 2005), there is limited work concerning delirium prevalence and physician detection rates in the emergency and/or acute care setting(s); furthermore, published data is predominantly from North America (Han et al., 2009, Han, Shintani, et al., 2010; Barron & Holmes, 2013; Han et al., 2017a). This gap in knowledge is especially critical given the differences in the breath (or management) of clinical-care provided in the emergency setting between the North American and European emergency systems and, consequently, its imprint on patient demographics (Rainer, 2000). Moreover, recommendations by the Society for Academic Emergency Medicine (SAEM) and by the American College of Emergency Physicians (ACEP) identified the detection of delirium in the ED as a high yield research objective (Terrell et al., 2009; Barron & Holmes, 2013). In 2010, the SAEM Task Force

identified four high-priority delirium research foci: (1) optimal methods of screening for and diagnosing delirium in the ED; (2) risk factors for delirium in the ED and interventions for prevention and moderation; (3) criteria for safe discharge for older ED patients with delirium; and (4) interventions to improve outcomes for older patients with delirium in the ED (Carpenter et al., 2020). Such recommendations deeply align with reality: it has been highlighted in the last decade that most importantly for emergency physicians is to recognize acute changes in mental status (Wilber & Ondrejka, 2016), and, with 57% of hospitalizations for older adults entering through ED, it is essential for emergency clinicians to understand how to screen, prevent, and treat patients with delirium (Greenwald et al., 2016; S. Lee et al., 2019).

4. Delirium Treatment in the ED

The touchstone of delirium treatment is to treat the underlying medical condition, or derangements (Lee et al., 2021). This is a complex task, that involves a multidomain approach that can be summarized as follows: addressing the often-multiple delirium triggers, correcting physiological disturbances, treating the symptoms of delirium including distress, communicating with patient and carers, and addressing the current and future risks linked with delirium (Wilson et al., 2020). The second principle of delirium treatment is to try first every non-pharmacological option. The nonpharmacy logical approaches available include reorientation and behavioral intervention (Fong et al., 2009). Pharmacological options are reserved for agitation with delirium and only after safety risk for both the patients and staff has been assessed (Lee et al., 2021).

The evidence that supports the treatment of delirium is not based on solid grounds. Interventions aimed at reducing the incidence and severity of delirium have been studied in various settings, and the evidence is the absence of ED research on which treatments are the most appropriate in the ED setting (Dahlstrom 2020). Furthermore, it is very difficult to compare interventions which were tested in different settings. For example, a meta-analyses in Intensive Care Units (ICU) failed to support that bundle interventions are effective in reducing ICU delirium prevalence and duration, but supports that bundle interventions are effective in reducing the proportion of patient-days with coma, hospital length of stay, and 28-day mortality (Zhang et al., 2020). On the other hand, outside the ICU, a Cochrane review showed that randomized trials and large cohort studies demonstrate that use of bundled, multicomponent nonpharmacological interventions, across health care settings, may reduce delirium occurrence by 30% or more (Siddiqi et al., 2016). In summary, there is a great body of research in the ICU that provides evidence for the efficacy of many non-pharmacologic interventions that can be

integrated into routine nursing care to significantly reduce the incidence and duration of delirium in the ICU (Sahawneh & Boss, 2021). But none of this evidence exists for the ED (Kennedy et al., 2021). More importantly, there are some principles which are foremost the mainstream for every practice in the ED. The agitated patient is, by no means, the most common situation where the concerns go beyond the patient itself to the stress felt by caregivers or institutional staff. Understanding who is the most concerned about the behaviors and why they are concerned is important. The challenge (and the goal) is to treat the patient first and then attend to the stress felt by caregivers or institutional staff (Agronin, 2007).

Specifically, we should highlight that most of the interventions that actually are currently done, and foremost in the ED, are pharmacological, being at the top the use of haloperidol. However, there is no proof, beyond not controlled studies, that haloperidol works either at the acute level or in prevention (Nikooie et al., 2019; Oh et al., 2020, Marra et al., 2021; Andersen-Ranberg et al., 2022). The matter gets more complex if we analyze delirium from a perspective of its main phenotypes, and looking to the other side of haloperidol, which was mainly studied in the hyperactive phenotype of delirium (Lodewijckx et al., 2021).

On this, it may be more relevant to consider The Care Perspective, which embraces an equally strong need to abolish the complacency of only detecting delirium, without building in essential linked processes for its prevention and effective treatment (Khachaturian et al., 2020). Delirium should, thus, be viewed in an integrated view that goes beyond the reductive vision of its biological facets. For instance, the Hospital elder life Program (HELP) is an innovative strategy, despite having been implemented for almost 30 years, of hospital care for elderly patients that uses tested delirium prevention strategies to improve overall quality of hospital care (Hospital Elder Life Program (HELP), n.d). This program demonstrates that delirium could be prevented in some patients hospitalized on the general medical and surgical floors (Khachaturian et al., 2020).Other examples of good practice come from the Administration for Community Living with the mission of maximizing the independence, well-being, and health of older adults, people with disabilities across the lifespan, and their families and caregivers (Administration for Community Living, n.d). Although this project focuses on dementia, it's by no means a global approach whose effort requires involvement from the wider community so that all stakeholders have visibility and voice, with the understanding that caregivers, family members, and healthcare professionals each see a different part of the problem (Khachaturian et al., 2020).

However, how we can approach this complex problem in the ED? One of the main conclusions is that the treatment of delirium in the ED is influenced by the high rates of misdiagnosis, so the focus on active screening, prevention, and intervention for those who are at risk for delirium and its associated complications are the next steps needed to improve care for older adults under our care and beyond (S. Lee et al., 2019). Prevention strategies (hydration, mobility, and nutrition) are often neglected in ED settings (Kennedy et al., 2021). Ready access to hydration and assistance from both medical staff and caregivers is recommended, as a previous study has demonstrated a reduction in the incidence of agitation (O'Keeffe & Lavan, 1996; S. Lee et al., 2019). The effective management of agitation should be a priority to every professional in the ED, and can be summarized by the TADA approach: Tolerate, Anticipate, Don't Agitate (Figure 3) (Kennedy et al., 2021).



Figure 3 Non-pharmacological approach to agitation in the ED, the TADA approach (Adapted from: Kennedy et al., 2021).

Regarding pharmacological treatment in the ED, these are based on findings which typically have focused on specific medication classes (e.g., antipsychotic medications), treatment settings (e.g.,

intensive care units), or patient populations (e.g., people who have undergone surgery), limiting generalizability to diverse clinical settings (Sadlonova et al., 2022).

Overall, there are varied proposed organized approaches for delirium in different settings (Liang et al., 2021; LaHue et al., 2021; Adams et al., 2022; Kim et al., 2022), although they are almost all for the ICU and general impatiens wards. For the ED, owing to the barriers for the development of research in delirium above mentioned, there is less evidence or foundations for the implementation of bundles of care specifically designed to delirium, in contrast with well described and defined paths by consensus for the approach on cerebrovascular events, acute coronary syndromes, trauma or sepsis, naming only some common clinical emergency scenarios. For that, here we chose to highlight an approach from the American Academy of Physicians. This approach was formulated to address the knowledge translation and implementation gaps that exist in the field of delirium (Kennedy et al., 2021). The recommendations — summarized by the acronym ADEPT (Table 6) — are based in a way that they are adaptable for different EDs, working as a framework. Furthermore, they are in accordance with the main objectives of prospectively evaluate the occurrence of delirium in the ED with CAM based diagnostic tools, focused synergistically on the identification of risks and prevention, and on a treatment based, as much as possible, in the identification of the underlying cause while avoiding actions or inactions that may worsen delirium (Shenvi et al., 2020).

Table 6 Practical approach for confusion and agitation in the elderly in the Emergency Department – ADEPT. (Adapted from: ACEP https://www.acep.org/patient-care/adept/ and http://eddelirium.org/what-to-do-when-delirium-is-detected/)

Action	Comments
ASSESS	
Perform a thorough evaluation to determine the underlying cause.	Evaluate for life-threatening causes of delirium using the mnemonic device **WHHHHIMPS: W**ernicke's disease or ethanol withdrawal; **H**ypoxia or hypercarbia; **H**ypoglycemia; **H**ypertensive encephalopathy; **H**yperthermia or hypothermia; **I**ntracerebral hemorrhage; **M**eningitis/encephalitis; **P**oisoning (whether exogenous or iatrogenic); **S**tatus epilepticus. For agitated patients, immediately assess safety risk for the patient and staff, and use the TADA approach. Assess for suicidal or homicidal ideation, auditory or visual hallucinations.
Perform a thorough physical exam.	Vital signs; Finger stick blood sugar should be obtained early. Fully expose the patient to examine the back, sacrum, genitalia, and feet for possible ulcers or infections. Assess for trauma, accidental, self-inflicted, or non-accidental. Neurological exam for signs of stroke, intra-cranial hemorrhage, or subclinical seizures.

Table 6. *Cont.*

Action	Comments
ASSESS	
The history, medication review, and collateral information are crucial.	Obtain the patient's medication history, including use of OTC medications, alcohol use, illicit drug use, recent changes or altered compliance with medications, and missed medications. High risk medications: sedatives, steroids, anti-histamines, anti-cholinergics, TCAs, muscle relaxants, or opioids. Contact family or facility staff familiar with the patient to gather collateral information and establish the patient's baseline mental status and level of functioning.
DIAGNOSE	
Screen for delirium in any agitated or confused older patient.	The hallmarks of delirium include acute onset, waxing and waning symptoms, inattention (eg. unable to recite days of the week backwards), change in cognition (eg new memory deficit, disorientation, perceptual disturbance, or disorganized thinking) or altered level of awareness (reduced orientation to environment such as RASS other than 0. Use the delirium triage score (DTS Calculator) and brief CAM (BCAM Calculator) or CAM-ICU to help identify patients with delirium.
Screen for underlying major neurocognitive disorder (dementia).	If the patient is able to cooperate, use a test such as the mini-cog: Ask the patient to repeat 3 items (banana, sunrise, chair), draw a face clock showing 10 minutes past 11, then recall the 3 items at 5 minutes. While dementia itself can cause behavioral changes, agitation, and psychotic symptoms, these symptoms should raise concern for delirium in a patient without a preexisting diagnosis of dementia.

Table 6. *Cont.*

Action	Comments
EVALUATE	
Perform a thorough, focused medical workup for agitation or confusion.	The workup should be driven by the history and physical exam. The leading causes of delirium are infections, intracranial abnormalities such as ischemic or hemorrhagic stroke and intra-cranial mass, electrolyte abnormalities, and medication complications or side effects. Recognize that the causes are often multi-factorial. Cause may be multi-factorial and include environmental factors such as a recent hospitalization or change in environment.
General tests for most patients will include:	BLOOD GLUCOSE; COMPLETE CELL COUNT; BASIC METABOLIC PANEL (hypo/hypernatremia, dehydration, AKI, hyper/hypokalemia, hypercalcemia); URINALYSIS AND CULTURE – UTI. EKG.
Specific, targeted testing and evaluation may include:	INFECTION: Chest X ray, Point-of-Care Ultrasonography, blood cultures, lactate, chest or abdomen/pelvis CT, LP; DRUG OR MEDICATION COMPLICATIONS: Specific drug levels (such as lithium, digoxin, acetaminophen, salicylate), venous blood gas; DRUG OR ALCOHOL ABUSE OR WITHDRAWAL: ethanol level, urine drug screen; ELECTROLYTE AND METABOLIC DERANGEMENTS: complete metabolic panel, liver function tests, venous blood gas, ammonia (which may be elevated due to various medications or liver failure); TRAUMA EVALUATION: CT head – if focal deficits, signs of head injury, severe headache, otherwise unexplained decreased level of arousal, or seizure; CARDIAC DISEASE: EKG, troponin, BNP, chest X-ray OTHER CONSIDERATIONS: venous blood gas for hypercarbia, thyroid stimulating hormone level if history/exam suggestive of hypo or hyperthyroidism, carboxyhemoglobin if other symptoms suggestive of possible CO toxicity. Core temperature if concern for hypo- or hyperthermia.

Table 6. *Cont.*

Action	Comments
	PREVENT
Individual patient measures to prevent or manage delirium:	Treat the underlying condition. Treat symptoms such as pain, nausea, constipation. Restart home meds unless contraindicated. Avoid the use of high-risk medications: benzodiazepines, sedatives, muscle-relaxants, ketamine, anti-histamines, high-dose anti-psychotics, and medications with anti-cholinergic properties. Normalize daily function: provide hydration, food, access to toileting, mobility, visual, hearing assists, day/night signals, and limit disruptions and unnecessary VS checks and BP cuff cycling. Avoid tethers unless necessary, including: Foley catheters, continuous IV infusions, BP cuffs, monitors Provide reassurance, redirection, distraction (eg activities or busy vests) and means for self-orientation (clocks, calendars, signs). Encourage family members or caregivers who demonstrate a calming presence to remain at bedside.
Hospital and systems-based measures to prevent or manage delirium:	Prevent injury. Lower beds, provide chairs, and use non slip floors or socks. Consider a sitter if available, for patients who are at high risk for falls and acutely agitated. Reduce ED length of stay. Avoid boarding in hallway beds and prioritize transfer to a floor bed once admission decision is made. ED MD and RN should communicate to inpatient MD and RN presence of dementia, delirium and/or agitation.
	TREAT
Take a multi-modal approach to treatment.	Treat the underlying medical condition or derangements identified on exam and testing. Treat symptoms such as pain, nausea, etc. Follow the prevention steps listed above.

Table 6. *Cont.*

Action	Comments
TREAT	
Use verbal de-escalation principles:	Respect personal space. Do not be provocative. Establish verbal contact. Be concise and use simple language. Identify the patient's wants and feelings. Listen closely to what the patient is saying. Agree or agree to disagree. Set clear limits. Offer choices and optimism. Debrief the patient and staff
If needed, start with oral Medications.	Go to table 7 to see Pharmacology therapy reserved for agitation with delirium
Carefully consider the use of IM or IV medications.	Go to table 7 to see Pharmacology therapy reserved for agitation with delirium
Avoid benzodiazepines if possible unless in withdrawal.	If a patient is chronically on benzodiazepines, do not stop these precipitously. Otherwise avoid the use of benzodiazepines if possible. They may cause prolonged sedation, paradoxical agitation, or worsening of delirium. If benzodiazepines are used, then the doses should be small, such as 0.5-1mg lorazepam* PO, IV, or IM.
Be cautious to prevent harm and minimize side effects.	Do not use medications such as diphenhydramine for agitation in elderly patients. It can cause anti-cholinergic side effects and prolonged sedation.

* lorazepam only available in oral route in Portugal

Table 7 Pharmacology therapy reserved for agitation with delirium (Adapted from: Rosen et al., 2015)

	Initial Dose	Redose	Max Dose	
Olanzapine	2,5mg PO/sl	Q2hr	30mg	Good choice if concerned about swallowing pill, history of EPS, long QT avoid if orthostatic hypotension
Risperidone	0,25mg PO	Q1hr	15mg	Good choice in demented patients avoid if long QT syndrome
Quetiapine	12,5mg PO	Q1,5hr	50mg	Good choice if concerned about history of EPS, long QT avoid if movement disorder, may cause sedation
Haloperidol	0,5mg IM	Q30min	10mg	Good choice if sedation desired avoid if Parkinson disease, history of EPS, long QT, seizures
Diazepam	5mg IV	Q15min	20mg	Good choice in EtOH withdrawal, rapid onset, can give IV or IM avoid if concern for hypotension, respiratory depression
Midazolam	2,5mg IV	Q15min	15mg	Good choice for procedural sedation, rapid onset
Oxazepam	15mg PO	Q6hr	50mg	Good choice if concerned about hepatic insufficiency, rapid onset

EPS, extrapyramidal symptoms; EtOH, ethanol

4.1. Punch Line

Realistic estimations in the ED place delirium prevalence ranges from 18% to 35% (Inouye et al., 2014; LaMantia et al., 2014; Kennedy et al., 2021). Contrasting with this high prevalence, delirium is only accurately diagnosed in 12%–35% of patients (Inouye et al., 2014). Delirium leads to adverse outcomes, including greater functional and cognitive decline at 6 months after discharge compared to those without delirium (Han et al., 2017b; Kennedy et al., 2021). Unidentified delirium is associated with a substantially increased risk of death, and among patients discharged from the ED, diagnosed delirium is associated with a nearly 5-fold increase in 30-day mortality (Israni et al., 2018; Kennedy et al., 2021). Delirium is costly. To illustrate the potential budgetary impact at a national level, inpatient delirium costs somewhere between $6.6 billion and $82.4 billion in the United States alone (in 2019 US$) (Kinchin et al., 2021).

Delirium has, thus, a prevalence and impact with huge personal, healthcare and economic costs, which makes it difficult to understand why these facts don't translate into action. It is clear that inadequate routine monitoring contributes to missed diagnosis of delirium. In the setting of failing to recognize the quality of practice such as geriatric ED, and age-friendly health system, the needs of effective delirium screening, treatment, and prevention programs are urgently needed (Lee et al., 2021). Mores so, the accuracy of estimates of the cost of disease-specific health-care services rely on the type and accuracy of data used for cost allocation (Kinchin et al., 2021). Thus, the magnitude of the effect of the costs in each particular system is, invariably, linked with the need of improving diagnosis, better measuring the burden and properly sensitizing for awareness. A consensus on quality outcomes in the ED for geriatric patients, as this is the most fragile and prone to delirium age group, involves delirium recognition, stressing that the consequences of an undetected delirium include progressive deterioration of functional and cognitive impairment, and an increased risk of mortality, thus early detection of delirium in the emergency care setting is essential (Schuster et al., 2020).

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CHAPTER II

Risk and Clinical-outcome indicators of delirium in an emergency department intermediate care unit (EDIMCU):an observational prospective study

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Risk and clinical-outcome indicators of delirium in an emergency department intermediate care unit (EDIMCU): an observational prospective study

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Abstract

Background: Identification of delirium in emergency departments (ED) is often underestimated; within EDs, studies on delirium assessment and relation with patient outcome in Intermediate Care Units (IMCU) appear missing in European hospital settings. Here we aimed to determine delirium prevalence in an EDIMCU (Hospital de Braga, Braga, Portugal) and assessed routine biochemical parameters that might be delirium indicators.

Methods: The study was prospective and observational. Sedation level was assessed via the Richmond Agitation-Sedation Scale and delirium status by the Confusion Assessment Method for the ICU. Information collected included age and gender, admission type, Charlson Comorbidity Index combined condition score (Charlson score), systemic inflammatory response syndrome criteria (SIRS), biochemical parameters (blood concentration of urea nitrogen, creatinine, hemoglobin, sodium and potassium, arterial blood gases, and other parameters as needed depending on clinical diagnosis) and EDIMCU length of stay (LOS). Statistical analyses were performed as appropriate to determine if baseline features differed between the 'Delirium' and 'No Delirium' groups. Multivariate logistic regression was performed to assess the effect of delirium on the 1-month outcome.

Results: Inclusion and exclusion criteria were met in 283 patients; 238 were evaluated at 1-month for outcome follow-up after EDIMCU discharge ("good" recovery without complications requiring hospitalization or institutionalization; "poor" institutionalization in permanent care-units/assisted-living or death). Delirium was diagnosed in 20.1% patients and was significantly associated with longer EDIMCU LOS. At admission, Delirium patients were significantly older and had significantly higher blood urea, creatinine and osmolarity levels and significantly lower hemoglobin levels, when compared with No Delirium patients. Delirium was an independent predictor of increased EDIMCU LOS (odds ratio 3.65, 95% CI 1.97-6.75) and poor outcome at 1-month after discharge (odds ratio 3.51, CI 1.84-6.70), adjusted for age, gender, admission type, presence of SIRS criteria, Charlson score and osmolarity at admission.

Conclusions: In an EDIMCU setting, delirium was associated with longer LOS and poor outcome at 1-month postdischarge. Altogether, findings support the need for delirium screening and management in emergency settings.

Keywords: Emergency department, Intermediate care units, Short stay units, High dependency units, Delirium, Confusion assessment method, Length of stay, Osmolarity

Backgrounds

As the acute diagnostic and treatment centers that provide a primary safety net with a 24/7 portal for rapid inpatient admission, modern emergency departments (ED) serve as a hub for emergency medical systems [1]. Within EDs, there is a rapid grow of Intermediate Care Units (IMCU) that are multi-purpose, high-dependency units [step-up from hospital wards and step-down from intensive care units (ICU)]. Patients admitted to high dependency units do not require full intensive care but need more services than those provided on a hospital ward [2,3], which calls for assiduous and rapid observation/ intervention as the patient's clinical condition evolves. The mean length of stay (LOS) in a standard EDIMCU is relatively short (24-72 hours) which may preclude/limit full information availability/assessment of the patient's "normal functioning". In this context, delirium may be a critical clinical factor to consider.

Delirium is defined as an acute change or fluctuation in mental status characterized by disorganized thinking and/or altered level of consciousness; importantly, it has a fluctuating course characterized by polymorphous and volatile symptoms [4]. Despite progress in the understanding of its clinical presentation, analysis of its clinical epidemiology, presentation and consequence to the overall clinical outcome remains complex [5-11]. In fact, although studies have indicated that delirium is a predictor of a longer hospital stay [5], there is limited work concerning delirium prevalence and physician detection rates in the emergency and/or acute care setting(s); furthermore, published data is predominantly from North America [9,12-14]. This gap in knowledge is especially critical given the differences in the breath (or management) of clinical-care provided in the emergency setting between the North American and European emergency systems and, consequently, its imprint on patient demographics [15]. Moreover, recent recommendations by the Society for Academic Emergency Medicine and by the American College of Emergency Physicians identified the detection of delirium in the ED as a high yield research objective [12]; nonetheless, although an increasing number of hospitals have created EDIMCUs, there are few data in the literature regarding delirium and outcomes in Eds and IMCUs [2,13] compared to the information in critically ill patients. In fact, with respect to delirium management, the few studies conducted in Europe included only 3% of the doctors working in high-dependency units [16]. This may be unrepresentative given the growing relevance of these units in emergency setting according to health policy reports [17].

Here, the main objective was to explore a relationship between delirium onset in an EDIMCU and patient outcome after discharge. For this, delirium occurrence among patients admitted to the EDIMCU

at the Hospital de Braga (Braga, Portugal) was assessed and related with clinical and biochemical information/parameters that served to orient the criteria for EDIMCU admission/care, together with EDIMCU admission type and LOS. Delirium was assessed with the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [9,14], given its ease of use, brevity and inter-rater reliability. Patient outcome was evaluated at 1-month after discharge.

Methods

EDIMCU

The study was conducted at the EDIMCU of the Hospital de Braga (Braga, Portugal), a University of Minho (Braga, Portugal) affiliated hospital (705-beds) that serves a population of 1,200,000 as a tertiary referral center. The Hospital de Braga has an ED with an annual census of approximately 175,000 visits; the ED and the EDIMCU are physically connected and the EDIMCU is part of the ED, sharing medical and nursing staff. The EDIMCU is a windowless 9-bed unit that receives patients from multiple intra and inter-hospital origin, including from the ED, surgical and medical wards (as a step-up unit), ICU (as a step-down unit), recovery operatory room, and other hospitals (without intermediate and/or intensive care units). The criteria for admission to the EDIMCU follow the Guidelines on Admission and Discharge for Adult Intermediate Care Units of the Society of Critical Medicine [18]. The unit provides non-invasive ventilation, invasive haemodynamic monitoring and inotrope infusion for high-risk medical and surgical patients; it does not provide renal replacement therapy or intracranial pressure monitoring. The standard nurse to patient ratio is 1:4 and a medical doctor is physically present in the unit (12-hour shifts).

Patients and study design

During a four-month period in April 2012 to July 2012, data was prospectively collected on all consecutive admissions to the EDIMCU (Hospital de Braga, Braga). Inclusion criteria included: patients aged 18 years or older admitted to the EDIMCU for more than 24hrs. Patients were excluded from the final analysis if the clinical staff was unable to assess for delirium using the Confusion Assessment Method for the ICU (CAM-ICU) at any time during the admission, including due to clinical evaluation refusal by the patient, inability to follow simple commands before acute illness onset, language communication barriers, dementia or other diagnosed neuropsychiatric disorder and coma. Exclusion criteria followed that reported in similar studies [9,19]. The delirium assessment analysis was completed for all patients who met the inclusion criteria (n = 283). Patients were followed at day 30

after hospital discharge (1-month follow-up); electronic charts were reviewed to ascertain the status of the patients, and when no up-to-date information was available patients or caregivers were contacted by telephone in an open-way interview. Outcomes were recorded as either "good" (recovery without complications requiring hospitalization or institutionalization) or "poor" (institutionalization in permanent care-units/assisted-living or death). For this observational study the Ethical Committee at Hospital de Braga approved the study protocol and waived informed consent. The study was non-interventional; therapies with regard to the clinical diagnosis, delirium and sedation state were left to the discretion of each patient's attending physician.

Data collection and study design

Data were recorded prospectively at least once per 12-hour shift as part of the routine care, starting in the first 12 hours of admission to the EDIMCU. EDIMCU nursing staff assessed sedation level via the Richmond Agitation-Sedation Scale (RASS) and delirium status via the CAM-ICU (Portuguese translation available at [20]), following the same methodology reported by Han et al. [9,14]) (see Additional files 1 and 2). The CAM-ICU is a modified version of the Confusion Assessment Method (CAM) that objectively reports on: i) acute onset of mental status changes or a fluctuating course, ii) inattention, iii) disorganized thinking, and iv) altered level of consciousness [21]. Because it is easy and brief (less than 2 minutes) to administer, the CAM-ICU is also ideal for the ED environment. The CAM-ICU has high sensitivity (93% to 100%), specificity (98% to 100%) and excellent inter-rater reliability (κ = 0.77 to 0.95) [10]. In patients who were CAM-ICU positive, the Richmond Agitation and Sedation Scale (RASS) was used to categorize the psychomotor subtype of delirium (RASS score between: +1 and +4, hyperactive delirium; 0 and -3, hypoactive delirium; with both positive and negative scores at 0 and 3 hrs, mixed type) [22,23]. Before the start of data collection, all staff that participated in patient evaluation was part of a 4-month training period coordinated by two staff members (as part of the hospital Quality Assurance Program). Training materials were provided by Vanderbilt University and included training manuals, didactic lectures, demonstrations, and direct practice of the assessment tools in patient scenarios. Practical clinical vignettes were conducted by the ED nursing staff to check the inter-rater reliability of the RASS and CAM-ICU. Patient information collected prospectively at the time of admission to the EDIMCU included: demographics (age and gender), admission diagnosis, Charlson Comorbidity Index combined condition and age-related score (which represents the sum of a weighted index that takes into account the number and seriousness of preexisting co-morbid conditions [24], Charlson score), and blood parameters (including blood concentration of urea nitrogen, creatinine, hemoglobin,

sodium and potassium, arterial blood gases, and other parameters as needed depending on clinical diagnosis; see Additional file 3). The EDIMCU protocol relies on blood analysis within 12 hours prior to admission. If patients do not have blood data in this time range and/or the clinical situation mandates prompt evaluation, blood parameters' analysis is conducted immediately at EDIMCU admission; therefore, all the biochemical data presented falls within the 12-hours range prior to admission. The usual parameters that serve to orient the criteria for admission and care were considered regarding delirium occurrence; furthermore, information collected at discharge from the EDIMCU included the biochemical parameters considered at admission and that regarding the place to where the patient was released to (family/home or institution). The diagnostic categories for EDIMCU admission, assessed by the patients' medical teams, represented the diagnostic category most representative of admission (cardiovascular, drug toxicity/ withdrawal, gastrointestinal, genitourinary, neurologic, haemato-oncologic, pulmonary, trauma/musculoskeletal and other). Admission type (emergency department, operating room, wards, intensive care unit, inter-hospital transfer) was also recorded. The Charlson score, systemic inflammatory response syndrome (SIRS) criteria (two or more of the following criteria: heart rate > 90 beats / min; body temperature < 36 or > 38°C; respiratory rate > 20 breaths / min; white blood cell count < 4x109 or > 12x109 cells / L [25]) and biochemical parameters were used as a surrogate for severity of illness. The acute physiology and chronic health evaluation II (APACHE II) was not applied; the APACHE II has not been validated for EDs or IMCU and the constraints of the EDIMCU context (balance of amount of prospective data collected versus feasibility) was considered.

Statistical analysis

Fisher's exact tests, exact chi-square tests, independentsamples Mann Whitney, independent-samples t-test and one-way ANOVA analysis were performed as appropriate to determine if baseline features differed between 'Delirium' and 'No Delirium' groups. Multivariate logistic regression was performed to assess the effect of delirium on the 1-month outcome after discharge from the EDIMCU. Age, gender, admission type, presence of SIRS criteria, Charlson score and osmolarity at admission were considered covariates. All statistical analyses were conducted using PASW statistics version 18.0 (SPSS)

Results

Baseline characteristics and delirium clinical outcome

Of the 298 patients screened, 283 patients met the inclusion criteria and 15 were excluded (Figure 1). Patients were divided in two groups: 'Delirium' (n = 57, 20.1%) and 'No Delirium' (n = 226, 79.9%). Baseline characteristics are presented in Table 1. Thirty-nine of the delirium cases (68.4%) were detected in the first 24 hours of admission, 13 (22.8%) between 24 and 72 hours, and 5 (8.8%) after 72 hours from admission. Thirty-two cases of delirium (56.1%) had the duration of 1 day, 14 cases (24.6%) 2 days, 7 cases (12.3%) 3 days, 3 cases 4 days (5.3%) and 1 case 6 days.

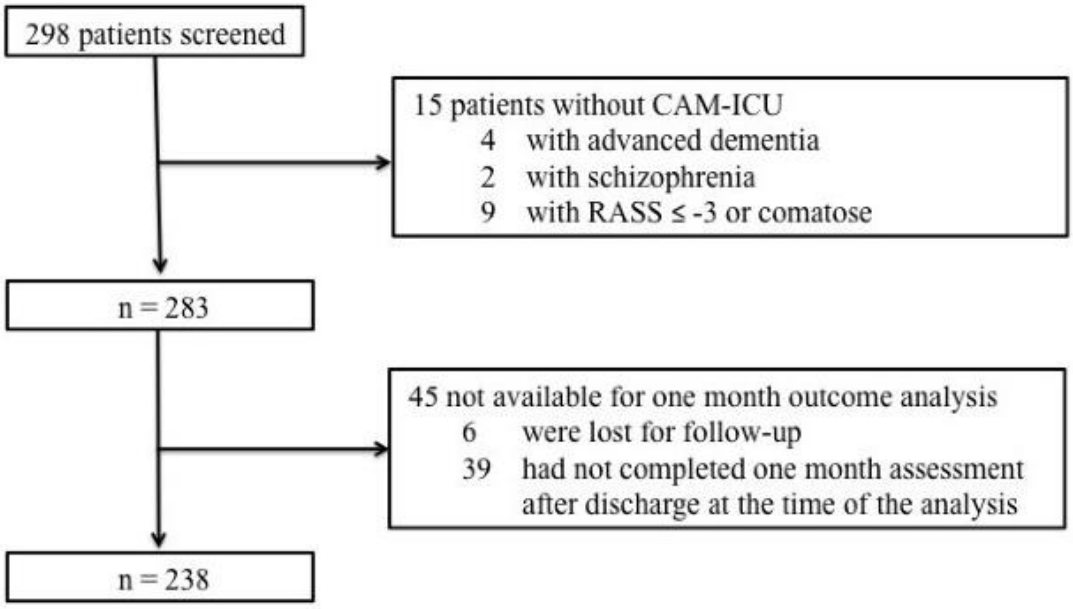


Figure 1 Patients meeting inclusion and exclusion criteria.

Table 1 Patient demographics and characteristics stratified by delirium status

	Delirium	No delirium	p-value
Patients, n (% total) [a]	57 (20.1)	226 (79.9)	
Characteristic			
Mean age, years (SD)	67.1 (± 16.0)	60.3 (± 17.6)	0.010
Female, n (% group)	18 (31.6)	18 (31.6)	0.278
SIRS criteria, %	38.6	23.5	0.028
Median Charlson (IQR)	4 (5)	3 (4)	0.039
Admission type (intra/inter hospital transfer category), n (% group; % origin) [b]			
Emergency department	28 (49.1; 23.0)	94 (41.6; 77.0)	
Operating room	6 (10.5; 6.4)	88 (38.9; 93.6)	
Wards	8 (14.0; 25.0)	24 (10.6; 75.0)	
Intensive care unit	7 (12.3; 63.6)	4 (1.8; 36.4)	
Inter-hospital transfer	8 (14.0; 33.3)	16 (7.1; 66.7)	
Emergency physician diagnosis by organ system, n (% group; % diagnosis) [c]			0.031
Cardiovascular	12 (21.1; 21.1)	45 (19.9; 78.9)	
Drug toxicity/withdrawal	2 (3.5; 33.3)	4 (1.8; 66.7)	
Gastrointestinal	11 (19.3; 11.7)	51 (22.6; 82.3)	
Genitourinary	6 (10.5; 22.2)	21 (9.3; 77.8)	
Neurologic	2 (3.5; 50.0)	2 (0.9; 50.0)	
Haemato-oncologic	4 (7.0; 11.8)	30 (13.3; 88.2)	
Pulmonary	13 (22.8; 36.1)	23 (10.2; 63.9)	
Trauma/musculoskeletal	7 (12.3; 21.9)	25 (11.1; 78.1)	
Other	0 (0.0; 0.0)	25 (11.1; 100.0)	

[a] Of the n = 298 patients enrolled, n = 15 were excluded due to dementia, neuropsychiatry illness or persistent coma (CAM-ICU assessment not conducted).

[b] Significant differences between ICU and ED (p = 0.008), OR (p < 0.001) and ward (p = 0.035), and between OR and ED (p = 0.016) and IHT (p = 0.020) (ANOVA, multiple comparisons Tukey post hoc HSD).

[c] Significant differences between Pulmonary and Other (p = 0.015) (ANOVA, multiple comparisons Tukey post hoc HSD). ED = emergency department, ICU = intensive care unit, IHT = inter-hospital transfer, IQR = interquartile range, OR = operating room; SD = standard deviation; SIRS = systemic inflammatory response syndrome.

Delirium patients were significantly older compared to No Delirium (mean 67.1 versus 60.2 years of age, p < 0.006), presented a higher percentage conforming to the SIRS criteria (38.6% versus 23.4%, p < 0.028) and had a higher Charlson score (median 4 versus 3, p < 0.039). Within the Delirium group no significant differences were noted regarding the time of delirium onset (after EDIMCU admission) and duration of delirium status; however, those with a mixed delirium subtype had a longer delirium status compared to hyper- and hypoactive delirium patients (p < 0.001) as well as a longer EDIMCU LOS between mixed and hypoactive (p < 0.009) (Table 2). No significant differences were noted between the Delirium and No Delirium groups regarding hospital LOS previous to EDIMCU admission; however, there was a significant difference between the Delirium and No Delirium groups for the EDIMCU LOS (median 1.0 versus 2.0 days, p < 0.001; odds ratio 3.65, 95% CI 1.97- 6.75). Significant differences were noted for type of hospital intra/inter transfer category prior to EDIMCU admission (p < 0.001); however, only ICU transfer (patients that were discharged from ICU and admitted in the

EDIMCU) appeared as possible risk factor for delirium (63.6% Delirium versus 36.4% No Delirium) (Table 1). Regarding clinical status, cardiovascular, pulmonary, gastrointestinal, and haemato-oncologic were the most common reasons for admission to the EDIMCU; occurrence rates of delirium were significantly different between groups ($p < 0.033$), but only patients with neurologic-related diagnosis appeared more likely to develop delirium (equal percentage between those with Delirium versus No Delirium) (Table 1).

Table 2 Delirium status classified by delirium subtype

	Hypoactive	Hyperactive	Mixed
Patients, n (% total)	22 (38.6)	23 (40.3)	12 (21.0)
Characteristic			
Mean age, years (SD)	65.6 (± 17.3)	67.3 (± 15.6)	69.2 (± 15.3)
Female, n (% group)	9 (40.9)	6 (26.1)	3 (25.0)
Mean length of delirium, days (SD)[a]	1.2 (± 0.4)	1.6 (± 0.8)	3.0 (± 1.3)
Median EDIMCU LOS, days (IQR)[b]	2.0 (0.25)	2.0 (2.0)	4.0 (5.0)

[a]Significant differences between Mixed and Hypoactive ($p < 0.001$) and Hyperactive ($p < 0.001$) (ANOVA, multiple comparisons Tukey post hoc HSD).
[b]bSignificant differences between Mixed and Hypoactive ($p = 0.009$) (Kruskal-Wallis for median, K independent samples, independent samples median test).

Biochemical parameters

For the analyzed biochemical parameters (see Additional file 3) at EDIMCU admission, when compared with No Delirium patients, Delirium patients had higher blood urea (mean 86.1 mg/dL versus 58.2 mg/dL, $p < 0.001$) and creatinine (mean 1.99 mg/dL versus 1.55 mg/dL, $p < 0.006$) at admission and lower hemoglobin concentration (mean 10.6 g/dL versus 11.3 g/dL, $p < 0.038$) (Table 3). Osmolarity and hemoglobin have a Pearson correlation value of 0.285 ($p < 0.001$). At discharge, delirium patients remained with significantly higher blood urea levels (mean 84.6 mg/dL versus 54.5 mg/dL, $p < 0.006$) and significantly lower hemoglobin concentrations (mean 10.0 g/dL versus 10.8 g/dL, $p < 0.03$) compared with No Delirium patients (Table 3). Osmolarity, a more accurate measure of (de)hydration than blood urea or sodium levels alone [26], was calculated from sodium, glucose and blood urea nitrogen levels at admission and was significantly different between groups (mean 320.55 mOsm/L versus 308.55 mOsm/L, $p = 0.001$).

Table 3 Biochemical parameters stratified by delirium status

	Delirium	No delirium	p-value
Biochemical parameters, mean (SD)[a]			
Blood urea at admission, mg/dL	86.11 (67.57)	58.22 (50.97)	0.001
Blood urea at discharge, mg/dL	84.56 (70.15)	54.54 (45.25)	0.006
Hemoglobin at admission, g/dL	10.5 (2.7)	11.3 (2.6)	0.038
Hemoglobin at discharge, g/dL	10.0 (1.7)	10.8 (2.2)	0.030
Creatinine at admission, mg/dL	1.99 (1.66)	1.55 (1.56)	0.006
Osmolarity, mOsm/L, mean (SD)[d]	320.55 (23.20)	308.74 (17.37)	0.001

[a]Only statistical significant results are presented. Urea admission (Delirium, n = 57; No Delirium, n = 216); urea discharge (Delirium, n = 55; No Delirium, n = 212); hemoglobin admission (Delirium, n = 56; No Delirium, n = 221); hemoglobin discharge (Delirium, n = 56; No Delirium, n = 222); creatinine admission (Delirium, n = 57; No Delirium, n = 218). [d]Plasma osmolarity measures the body's electrolyte-water balance [osmolarity = (2*sodium) + (glucose/18) + (blood urea nitrogen/3)], normal range 270-310 mOsm/L. Osmolarity calculated only for patients with all variable (sodium, glucose and blood urea) measurements at admission (Delirium,n = 48; No Delirium, n = 175). SD = standard deviation.

One-month outcomes and multivariate analysis

At the 1-month outcome analysis 51 patients (17.1%) were excluded (patients with no contact and/or clinical information at 1-month after discharge); a total of 50 patients from the Delirium group and 188 from No Delirium group were evaluated (Figure 1 and Table 4). In the Delirium group mortality at the 1-month evaluation was 30% (combined death in the EDICUM and death after discharge; respectively, n = 7 and n = 8 for each setting) versus 10% for the No Delirium group (combined death in the EDICUM and death after discharge; respectively, n = 3 and n = 16) ($p < 0.001$). Furthermore, 26% patients were institutionalized versus 16.5% of the No Delirium group ($p = 0.022$). The estimated odds ratio for a poor outcome at 1-month associated with delirium status was 3.51 (CI 1.842 – 6.698). Delirium was independently associated with poor outcome at 1-month, defined as global mortality and/or institutionalization (multivariate logistic regression to assess the effect of delirium controlling for age, gender, admission type, SIRS criteria, Charlson score and osmolarity at admission).

Table 4 Clinical outcome and mortality at one-month assessment and multinomial logistical regression analysis results

Outcome	Delirium	No delirium	Odds ratio (CI)	p-value
1-month, n (% group, % total) [a]			3.51 (CI 1.84-6.70)	< 0.001
Good	22 (44.0; 9.2)	138 (73.4; 58.0)		< 0.001
Poor[b]	28 (56.0; 11.8)	50 (26.6; 21.0)		
Poor, n (% group, % total) [b,c]				
Death	15 (30.0; 19.2)	19 (10.1; 24.4)		< 0.001
Institutionalization	13 (26.0; 16.7)	31 (16.5; 39.7)		0.022
EDIMCU LOS, days, median (IQR)	2.0 (2.5)	1.0 (1.0)	3.65 (CI 1.97-6.75)	< 0.001
Logistic regression parameter	**Coeff. (SE)**		**Odds ratio (CI)**	**p-value**
Age	−0.00 (0.14)		1.00 (CI 0.97-1.02)	0.798
Gender	0.66 (0.64)		1.93 (CI 0.94-3.98)	0.075
Admission type	−0.31 (0.13)		0.57 (CI 0.57-0.95)	0.020
Charlson score	−0.08 (0.08)		0.93 (CI 0.79-1.08)	0.344
SIRS	−0.64 (0.38)		0.53 (CI 0.25-1.12)	0.095
Osmolarity	0.01 (0.01)		1.01 (CI 0.99-1.02)	0.602
Delirium	1.28 (0.40)		3.60 (CI 1.63-7.96)	0.002
Intercept	- 0.72 (3.03)			0.811

[a]Total sample n = 238, n = 6 patients were lost (no contact information or consult), n = 45 did not complete 1-month follow-up. [b]Total poor outcome sample n = 78, poor outcome refers to mortality or institutionalization after discharge (permanent care units), with no significant difference between these. [c]No significant difference in mortality between while in EDICUM or after discharge. Charlson score Charlson comorbidity index combined condition score; CI confidence interval (95% confidence interval for the odds ratio); Coeff.coefficient expressed in logits; IQR interquartile range; LOS length of stay; SE standard error; SIRS systemic inflammatory response syndrome criteria.

Discussion

To our knowledge, this is the first report on delirium occurrence in a European EDIMCU. Results show 20.1% delirium prevalence (delirium patients significantly older than no delirium patients), with a significant relationship between delirium and mortality and LOS in the unit, and between delirium and global mortality and institutionalization at 1-month after discharge (all measures of poor outcomes). ICU transfer (at EDIMCU admission) appeared as a possible risk factor. Although not reaching statistical significance for delirium onset, it should be noted that 49.1% of the delirium patients were admitted from the ED (the ED and the EDIMCU are inter-supporting services at the Hospital de Braga and are physically bound in the same hospital wing), representing a total of approximately 1 in each 4 ED-origin patients developing delirium. The primary admission diagnosis and/or medical vs. surgical cases did not appear to impact delirium onset. The significant positive relationship between delirium and EDIMCU LOS is in accordance with results of other studies conducted in EDs [7,27]; however, no significant difference in hospital LOS prior to EDIMCU admission was noted between delirium and non-delirium patients. The majority of delirium episodes occurred in the first 24 hour of admission, highlighting the importance of early screening in high-dependency units particularly, as was the case in this study, when

a measure (information) on cognitive status prior to admission is not available. This observation is in line with other reports on delirium in the ED; it is advised screening in the first 12 hours of admission, to minimize extraneous factors that may artificially cause (new) onset delirium from prolonged exposure to known delirium precipitants (e.g. lack of windows, broken circadian rhythms with unscheduled admissions) [9]. Furthermore, our results indicate that screening should include assessment of routine biochemical parameters that may reflect dehydration, including blood urea, creatinine and osmolarity, as delirium indicators (these were significantly different between the Delirium and No Delirium groups). Results in these measures are more relevant in combination with the SIRS criteria and Charlson score; delirium patients presented significantly higher scores. Finally, multivariate analysis (controlling for age and gender, admission type, SIRS criteria, Charlson score and osmolarity at admission) significantly indicated that delirium status in the EDIMCU, independently of duration, relates with poor outcome at 1-month (that is, mortality or institutionalization in care-units). Altogether, the results of the analysis are particularly relevant as the routine practice of delirium screening in the EDs remains limited and there are few data from the EDs and IMCUs literature regarding delirium and outcomes [2,13]. Here, the findings point to the main factors governing delirium in an acute setting: advanced age, admission type and dehydratation. As multicomponent strategies for the prevention of delirium have been developed for the hospital setting [28], it is unclear whether or not initiation of these interventions in the ED would improve outcomes. Of note, many of these multicomponent interventions require extensive resources and may not be feasible to perform in the ED setting. Nonetheless, some evidence indicates that increasing awareness of delirium through a brief and inexpensive education of staff on acute medical wards improves the rate of delirium detection [29,30]; this would be particularly optimal if associated with appropriate national guidelines and curriculums [29]. Therefore, simpler early detectiondirected strategies focused on factors readily detectable by ED nursing and medical teams may probably be more effective than complex interventions requiring rigorous screening and specialized nursing [7,12,28]. Considering the substantial overlap between intermediate-care patients and less severely ill ICU patients [2], the rate detected in our cohort probably represents a continuum from severely ill to less severe patients. Of economic repercussion, the growing use of EDs, cited as a key contributor to rising health care costs, has become a leading target of health care reform [1]; therefore, the finding in EDIMCU that delirium is a predictor of longer LOS and mortality, and as well a predictor of greater level of dependency, is of particular relevance.

Critical care services vary between countries in both numbers of beds and volume of admissions, rendering in some cases distinction between intensive care and intermediate care units difficult [2,31,32]; importantly in the context of this study, is the fact that EDIMCU-type high-dependency units are much more common in Europe than in the US. The clinical features of high-dependency patients (as those in EDIMCU) are similar, but not identical, to those of less severely ill ICU monitor patients; therefore, comparisons should be adjusted for characteristics that previously have been shown to influence these outcomes [2]. Results of this cohort of highdependency patients bounded to the ED require further analysis, particularly in comparison with non-ventilated ICU patients; however, routine daily delirium monitoring is already justified [5]. Ultimately, analysis of delirium rates and their outcome in the EDIMCU setting will help in the planning and debate over the roles and capabilities of this type of acute care areas.

Conclusions

Delirium developed in approximately one fifth of the patients in the EDIMCU and was positively associated with age, longer EDIMCU LOS and poor outcome at 1-month after discharge (considering mortality and institutionalization, isolated and combined). Interestingly, although patients from ICU appeared to be at a greater delirium risk, delirium was not associated with the nature of admission. The main risk factors related with (de) hydration biochemical parameters.

Key messages

- Studies on delirium prevalence and impact on patient outcome are missing in high-dependency EDIMCUs;
- Age, SIRS criteria, Charlson score and creatinine, blood urea, hemoglobin and osmolarity levels are indicators of delirium;
- Delirium is significantly associated with a longer EDIMCU LOS;
- Delirium is an independent risk factor of poor outcome (institutionalization and mortality) at 1-month after EDIMCU discharge;
- Further research is warranted to determine whether early detection alters outcome.

Abbreviations

APACHE II: Acute physiology and chronic health evaluation II; CAMICU: Confusion assessment method for the intensive care unit; CI: Confidence interval; ED: Emergency department; EDIMCU: Emergency department intermediate care unit; ICU: Intensive care unit; IQR: Interquartile range; LOS: Length of stay; RASS: Richmond agitation-sedation scale; SD: Standard deviation; SIRS: Systemic inflammatory response syndrome.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Each author of this manuscript has: made substantial contributions to conception and design, acquisition of data, and the analysis or interpretation of data; been involved in drafting the article and revising it critically for important intellectual content; and given final approval of the submitted version to be published. All authors read and approved the final manuscript.

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CHAPTER III

Delirium Diagnostic and Screening Instruments in the Emergency Department: An Up-to-Date Systematic Review

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Delirium Diagnostic and Screening Instruments in the Emergency Department: An Up-to-Date Systematic Review

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Abstract:

Background: Emergency care systems are at the core of modern healthcare and are the "point-of-entry/admission" into the hospital for many older/elderly patients. Among these, it is estimated that 15% to 30% will have delirium on admission and that over 50% will develop it during their stay. However, appropriate delirium diagnostic and screening still remains a critical area of need. The goal of this review is to update the field, exploring target areas in screening methods for delirium in the Emergency Department (ED), and/or acute care units, in the older population. Methods: A systematic review was conducted to search screening/diagnostic methods for delirium in the ED and/or acute care units within the ED. Results: Seven different scales were identified. Of the identified instruments, the Confusion Assessment Method (CAM) for the Intense Care Unit (CAM-ICU) was the most widely used. Of note, a brief two-step approach for delirium surveillance was defined with the Delirium Triage Screen (DTS) and the Brief Confusion Assessment Method (bCAM), and the diagnostic accuracy of the Richmond Agitation-Sedation Scale (RASS) for delirium had a good sensitivity and specificity in older patients. Conclusion: The CAM-ICU appears as the potential reference standard for use in the ED, but research in a global approach of evaluation of actual and past cognitive changes is still warranted.

Keywords: delirium; emergency department; CAM-ICU; organic brain syndrome; RASS

1. Overview

Emergency care systems are at the core of modern healthcare. Their primary role is to provide high-quality care to patients regardless of when they need medical help or what they present with [1]. In the Emergency Department (ED) (and/or intermediate or acute care units within these), much of the problem regarding delirium incidence and prevalence relates, in great part, to the unique environment: intense time demands on providers and high volume of patients. Together, these aspects can both: (i) render the caring for older adults challenging; and (ii) hinder the use and validation of screening tools. This occurs despite any positive impact that this latter work would in itself yield, including early identification of delirium and translation into appropriate treatment measures. Regarding delirium, the problem is compounded when considering that the older/elderly population uses emergency care facilities more often than younger individuals [2] and age is one of the principal risk factors for delirium onset. Studies of delirium prevalence have indicated that 15% to 30% of the older/elderly population will have delirium on admission to hospital and over 50% will develop it during their stay (for example, [3,4]). These data are collaborated by a recent and very relevant review by Inouye et al. (2014)

indicating that delirium is present in 8%–17% of all elderly people and 40% of nursing home residents, with the authors also noting that presence of delirium in the community is rather low (1%–2%) but onset is conducive to an ED admission. Delirium associates with relevant indicators such as increased mortality, including after discharge from the hospital, and its presence in the emergency department (ED) is a predictor of a longer hospital stay [3–5].

Still, despite the findings, there has been surprisingly a lack of studies in the ED context. For instance, to our knowledge, to date, there are no studies on delirium incidence in the ED amongst older/elderly individuals. This is also particularly true concerning physician detection rates and efficacious detection methods, such that the detection of delirium in the ED continues to be indicated as a "high yield" research objective [4]. It is, furthermore, also identified as a quality indicator of geriatric assessment in the ED [6]. Stemming from this need, LaMantia et al. (2014) previously published a relevant systematic review on screening tools of delirium in the ED. Since then, there have been other significant advances which meet what the authors had indicated as necessary targets in order to move the field of delirium identification and management forward within the ED [6]. Chiefly amongst these advances: (i) Han and colleagues validated the Confusion Assessment Method for the Intense Care Unit (CAM-ICU) for the ED [7], continuing work on brief tools for delirium in this setting, which responds to the need for more rapid assessments of acute brain function; and (ii) a novel screening approach was tested using the Richmond Agitation-Sedation Scale (RASS), a brief attention test followed by an adaptation of the CAM-ICU [8,9].

Here, providing a further update to the advances in the field, the goal of this review is to explore target areas in screening methods for delirium in the ED and/or acute care units, with focused attention on rapid screening tools adapted to these settings. More so, we seek to inform in terms of time consumed administering the available instruments, which is one of the more important challenges to do research in delirium in the ED. The use of psychometric characteristics to better guide the emergency care provider in choosing the screening tool, and practical cues on the application of the screening tools to help the clinician better choose depending on emergency load, are also considered.

2. Literature Review

A systematic search of the literature was conducted in the Science Direct and MEDLINE/PubMed databases using a combination ofMeSHterms “organic brain syndrome”, “delirium”, “acute confusional state”, “emergency” and “emergency department”. The databases were searched from their inception to November 2015 for relevant articles published in English, French, Spanish and Portuguese. The term “organic brain syndrome” was included to consider previous literature when the term was commonly used in referring to delirium. Two separate researchers (J.M., an emergency physician, and T.C.C., a psychologist) conducted independently the search. The generated lists were compared to obtain a compiled list of potential studies for inclusion. The PICOT framework and the search strategy of LaMantia et al. (2014) [6] were considered.

Only prospective studies of patients aged 65 years of age and older were considered, and only if the characteristics of the used (screening/diagnostic) instruments were described. Out-of-hospital evaluations and interventional studies (on delirium) were excluded from the review, as were commentaries and/or author opinions on neuropsychological (delirium) instruments. Acute patient units and/or Intermediate Units were only considered if integrated and/or physically located (with)in the ED, given that in great part these are found to function with the same staff and constraints of the ED. Of note, the definition of Acute Care Unit is not uniform across continents and countries, including varying in what kind of patients are admitted and when. If used, the Diagnostic and Statistical Manual of Mental Disorders (DSM) was not considered a screening instrument in itself, but rather the gold standard criteria (including if applied by non-psychiatrists). All tools used to assess assess delirium (both diagnostic and screening) were considered in the analysis; in the final quantitative step, all tools were supported by validation studies.

Summarily, a total of 714 citation titles were identified in the search. Of these, 707 potentially relevant abstracts were screened, of which 141 articles were selected for detailed analysis (i.e., met the exclusion and inclusion criteria). Of the full articles read and assessed for eligibility, a final 30 were included in the systematic review. From the analysis, a total of seven delirium screening tools were identified as being used in the ED. The search procedure is summarized in Figure 1, following the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)” flow diagram template. Table 1 summarizes the instruments, including information on author (date of publication), population, type of study, setting (country), purpose and main findings of the work. Table 2 summarizes the (original) author, validation sample/study, administration time, sensitivity and specificity measures,

and additional validation studies in other countries, of the delirium screening instruments here identified.

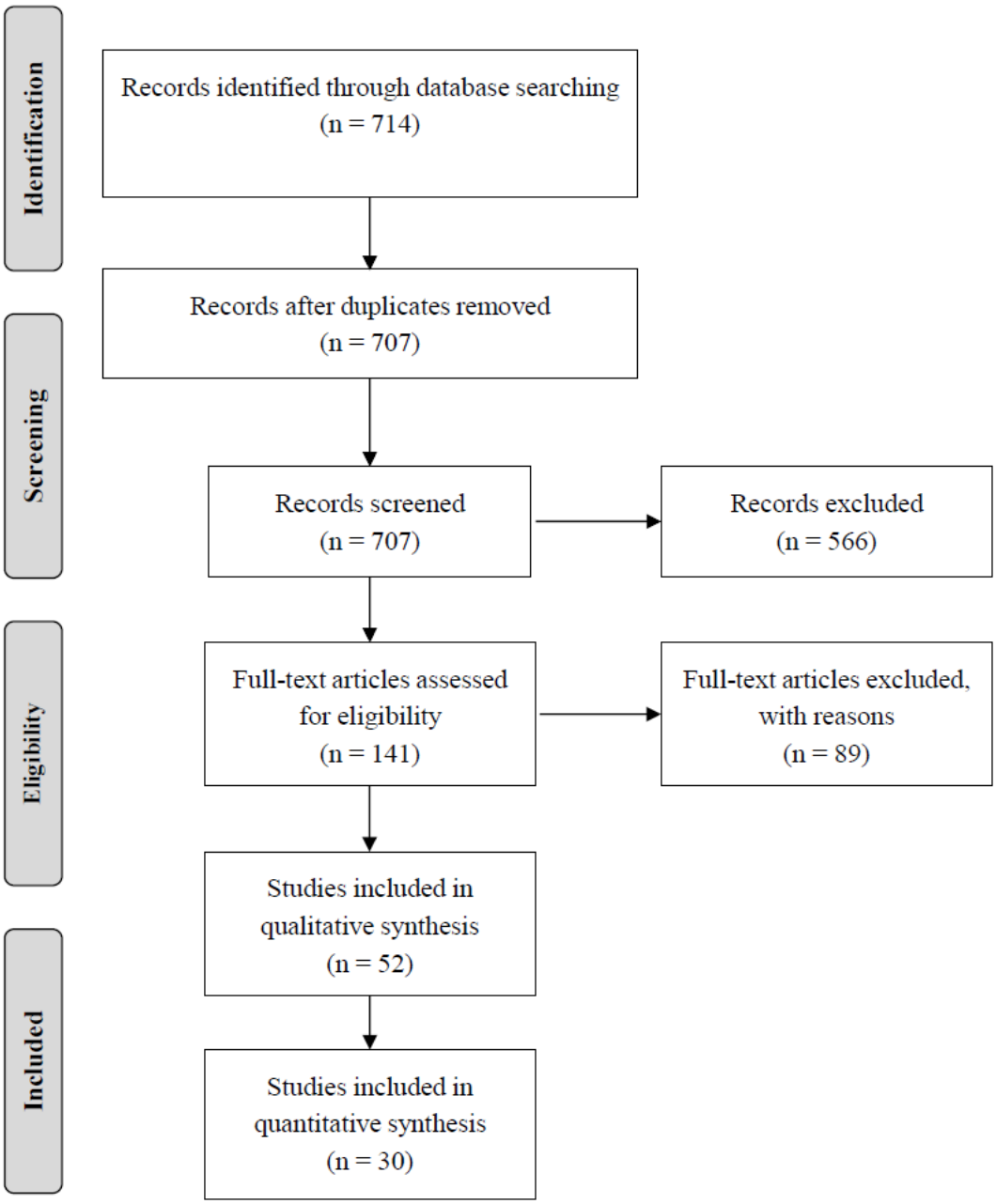


Figure 1 Flow diagram of the literature review

Table 1 Summary of studies using delirium screening tests.

Author (Date of Publication)	Population	Type of Study	Setting (Country)	Purposes
Confusion Assessment Method (CAM) (Inouye et al. 1990) [8]				
Lewis et al. (1995) [9]	385 elderly patients	Cohort study	Emergency department (Canada)	Determine the likely presence of delirium and to examine the sensitivity of emergency physician's routine histories and physical evaluations to identify this disorder.
Élie et al. (2000) [10]	447 elderly patients	Comparative study	Primary acute care University-affiliated hospital (Canada)	Determine the prevalence of delirium in emergency department and the sensitivity and specificity of a conventional assessment by a physician for the detection of delirium.
Fabbri et al. (2001) [11]	100 elderly patients	Validation study	Emergency Room of a teaching hospital (Brazil)	Investigate CAM's reliability of its Brazilian version as well as its validity.
Monette et al. (2001) [12]	116 elderly patients	Prospective study	Emergency Room (Canada)	Compare the results of the CAM assessment obtained by a trained non-physician interviewer and those obtained by a geriatrician.
Hustey et al. (2002) [13]	297 elderly patients	Prospective observational study	Urban teaching hospital emergency department (United States)	Determine the prevalence of mental status impairment in elderly emergency department and to assess documentation of and referrals by emergency physicians for mental status impairment after discharge
Hustey et al. (2003) [14]	271 elderly patients Family members and other people close to the participant were also interviewed regarding CAM to account for the fluctuating nature of delirium	Prospective cross-sectional study	Urban teaching hospital emergency department (United States)	Determine the effect of screening evaluations for mental status impairment and prospectively assess recognition of mental status by emergency physicians.

Table 1. *Cont.*

Author (Date of Publication)	Population	Type of Study	Setting (Country)	Purposes
Kakuma et al. (2003) [15]	30 delirious and 77 nondelirious older individuals Family members and other people close to the participant were also interviewed regarding other measures to account for premorbid cognitive status and functional abilities.	Prospective study with 18 months of follow-up	Emergency department (Canada)	Determine if prevalent delirium is an independent predictor of mortality in older patients seen in the emergency department and discharged home without admission.
Naughton et al. (2005) [16]	110 elderly patients	Pretest and posttest study	University-affiliated hospital (United States)	Admit cognitively impaired and older individuals with delirium from the emergency department to an acute geriatric unit and improve outcomes for cognitively impaired and delirious older adults
Vida et al. (2006) [17]	259 elderly patients	Prospective cohort study	Emergency Department of University teaching and General Hospitals (Canada)	Determine if patients with delirium show poorer ADL, BADL or IADL at 6-, 12- and 18-month points than those without delirium and determine if delirium is an independent predictor of poorer ADL, IADL and BADL.
Hare et al. (2008) [18]	28 elderly patients	Audit	Emergency Department (Australia)	Determine if routine cognitive screening of elderly patients in emergency department could lead to early identification of delirium.
Hare et al. (2014) [19]	320 older patients	Prospective observational study	Emergency Department (Australia)	Derive a brief screening tool to predict the presence of delirium
Kennedy et al. (2014) [20]	700 elderly patients	Prospective observational study	Urban tertiary care emergency department (United States)	Create a risk prediction rule for emergency department delirium and compare mortality rates and resource utilization of delirious versus non-delirious elderly patients
Singler et al. (2014) [21]	133 elderly patients	Prospective single center cohort study	Interdisciplinary emergency department of an university-affiliated hospital (Germany)	Assess the prevalence of delirium and its detection by emergency department physicians, and identify delirium-associated patient characteristics

Table 1. *Cont.*

Author (Date of Publication)	Population	Type of Study	Setting (Country)	Purposes
Modified Confusion Assessment Method for the Emergency Department (mCAM-ED) (Grossmann et al. 2014) [22]				
Grossmann et al. (2014) [22]	207 elderly patients	Prospective observational study	Emergency Department of the University Hospital Basel, (Switzerland)	Investigate whether there is a need for a standardized delirium screening and assessment instrument in the ED; evaluate the feasibility of a new algorithm for delirium screening, detection and managementof delirium in the ED; assess interraterreliability of the developed mCAM-ED.
Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) (Ely et al. 2001) [23]				
Han et al. (2009) [24]	341 elderly patients	Prospective cross-sectional study	Tertiary care academic emergency department (United States)	Determine whether nursing home patients are more likely than non-nursing home patients to present to the emergency department with delirium and to explore how variations in their delirium risk facto profiles contribute to this association.
Han et al. (2009) [24]	303 elderly patients	Prospective cross-sectional study	Tertiary care, academic emergency department (United States)	Determine how often delirium is missed in emergency department; identify delirium risk factors in older emergency department patients; to characterizes delirium by psychomotor subtypes in the emergency department setting.
Han et al. (2010) [4]	629 elderly patients	Prospective cohort study	Tertiary care, academic emergency department (United States)	Determine if delirium is an independent predictor of 6-month mortality and assess if this relationship is modified by nursing home residence.
Han et al. (2011) [25]	202 elderly patients	Cross-sectional study	Tertiary care, academic emergency department (United States)	Determine how delirium and dementia affect the accuracy of the presenting disease and discharge instruction comprehension in older emergency department

Table 1. *Cont.*

Author (Date of Publication)	Population	Type of Study	Setting (Country)	Purposes
Han et al. (2011) [26]	628 elderly patients	Prospective cohort study	Tertiary care, academic emergency department (United States)	Determine if delirium in the emergency department was an independent predictor of prolonged hospital length of stay
Suffoletto et al. (2013) [27]	259 elderly patients	Prospective study	Teaching hospital emergency departments (United States)	Study whether emergency physicians identify delirium and examine each of the four individual features of delirium separately to determine the variation in identification across features
Mariz et al. (2013) [5]	283 adult patients	Prospective cohort study	Urban tertiary care hospital (Portugal)	To determine delirium prevalence in an EDIMCU and assess routine biochemical parameters that might influence delirium occurrence
Han et al. (2014) [7]	406 elderly patients	Prospective observational study	Tertiary care, academic emergency department (United States)	Determine CAM-ICU validity and reliability in older emergency department patients
Sri-on et al. (2015) [28]	232 elderly patients	Prospective cross-sectional study	Emergency department of an urban tertiary care hospital (Thailand)	Determine the prevalence of delirium and identify risk factors and short-term outcomes in delirious elderly emergency department patients.
Hsieh et al. (2015) [29]	260 elderly patients	Prospective cohort study	Urban tertiary care hospital (United States)	Measure the prevalence and incidence of delirium in older adults as they transition from the emergency department to the inpatient ward; determine the association between delirium during early hospitalization and subsequent clinical deterioration

Table 1. *Cont.*

Author (Date of Publication)	Population	Type of Study	Setting (Country)	Purposes
Delirium Triage Screen (DTS) (Han et al. 2013) [9]				
Han et al. (2013) [30]	406 elderly patients	Prospective observational study	Tertiary care, academic emergency department (United States)	Determine the diagnostic performances of novel assessments using the psychiatrist's assessment as the reference standard
Brief Confusion Assessment Method (bCAM) (Han et al. 2013) [30]				
Han et al. (2013) [30]	406 elderly patients	Prospective observational study	Tertiary care, academic emergency department (United States)	Determine the diagnostic performances of novel assessments using the psychiatrist's evaluation as the reference standard
Rizzi et al. (2015) [31]	239 elderly patients	Observational, prospective, multicentric and cross-sectional study	Emergency department (Spain)	Investigate the presence of delirium at admission in patients with decompensated heart failure, identify their risk factors and analyze their impact on clinical outcomes
Neelon and Champagne Confusion Scale (NEECHAM) (Neelon, 1996) [32]				
Almató et al. (2012) [33]	90 elderly patients	Prospective observational study	Emergency department (Spain)	Estimate the prevalence of delirium in the emergency monitoring area and analyze the association between the presence of delirium with risk factors and precipitants.
Richmond Agitation-Sedation Scale (RASS) (Sessler et al. 2002) [34]				
Han et al. (2014) [35]	1084 non-comatose elderly patients	Prospective cohort study	Tertiary care, academic emergency department (United States)	Determine if impaired arousal at initial presentation in older acutely ill patients predicted 6-month mortality and if this relationship was present in the absence of delirium.
Han et al. (2015) [36]	406 elderly patients	Prospective observational study	Tertiary care, academic emergency department (United States)	Determine the diagnostic accuracy of the RASS for delirium

Table 2 Summary of the psychometric aspects of validated delirium screening instruments

Name and Author	Validation Sample	Country of Validation	Number of Items/Criteria; Administration Time	Sensitivity; Specificity	Validation in Other Countries
CAM (Inouye et al. 1990) [8]	56 patients	USA	9 criteria; 20 min	94% to 100%; 90% to 95%	Brazil, Finland, France, Germany, Portugal, Spain, Thailand
mCAM-ED (Grossmann et al. 2014) [22]	207 elderly patients	Switzerland	3 step assessment; 4–6 min	Small sample not able to calculate with accuracy	NF
CAM-ICU (Han et al. 2014) [7]	406 elderly patients	USA	4 criteria; 2–5 min	68% to 72%; 98.6%	NF
DTS (Han et al. 2013) [9]	406 patients	USA	Two-step assessment; 20 s	98%; 55%	NF
bCAM (Han et al. 2013) [30]	406 patients	USA	4 criteria; 2 min	78% to 84%; 96% to 97%	NF
NEECHAM (Neelon, 1996) [32]	426 elderly patients	USA	9 items; 10 min	95%; 78%	Portugal; Sweden; Belgium
RASS (Sessler et al. 2002) [34]	293 ICU patients	USA	Ten-step assessment; 30–60 s	99%; 64%	Brazil; Germany; Iran; Spain

CAM = Confusion Assessment Method; CAM-ICU = Confusion Assessment Method for the Intensive Care Unit; mCAM-ED = Modified Confusion Assessment Method for the Emergency Department; BCAM = Brief Confusion Assessment Method; RASS = Richmond Agitation-Sedation Scale; DTS = Delirium Triage Scale; OBS = Organic Brain Syndrome Scale; NEECHAM = Neelon and Champagne Confusion Scale; NF = Not Found, unable to find any published peer-reviewed articles regarding instrument validations in other countries.

3. Delirium Screening Instruments in the ED and/or in Acute Care Units

A total of seven different instruments were identified for delirium screening/diagnostic: Confusion Assessment Method (CAM); modified Confusion Assessment Method for the Emergency Department (mCAM-ED); Confusion Assessment Method for the Intensive Care Unit (CAM-ICU); Delirium Triage Screen (DTS); Brief Confusion Assessment Method (bCAM); Neelon and Champagne Confusion Scale (NEECHAM); and the Richmond Agitation Sedation Scale (RAAS). The latter was considered in the analysis; albeit being a sedation scale not directed for delirium assessment, there are enough data to consider it a screening scale with a good psychometric performance [36]. The DTS and the bCAM were considered as separate instruments, although it is proposed as a two-step approach in the ED environment [30].

3.1. Confusion Assessment Method (CAM)

The CAM [8] is overall considered the standardized, structured instrument to identify patients with delirium. It utilizes observation and interaction with the patient to provide data to which a simple algorithm can be applied to determine if delirium is present or not. Specifically, the CAM includes two parts. Part one screens for overall cognitive impairment and part two considers the following features: (1) acute onset of mental status changes or a fluctuating course; (2) inattention; (3) disorganized thinking; and (4) altered level of consciousness. A positive diagnosis of delirium requires the presence of Features (1) and (2), and either Feature (3) or (4). The instrument was validated for use by geriatricians and it takes approximately 5 min to fill out. Using psychiatric assessment as the gold standard, the CAM has shown a sensitivity of 94% to 100%, a specificity of 90% to 95% for the detection of delirium and a high inter-observer reliability [8]. This tool is translated and validated for use in various non-English speaking populations. Despite the CAM's possibility to identify the presence or absence of delirium in a quick and easy way, it does not assess the severity of the condition.

3.2. Modified Confusion Assessment Method for the Emergency Department (mCAM-ED)

The mCAM-ED is an algorithm developed by Grossman et al. (2014) [22] for delirium screening, detection and management in older ED patients. An integral part of the algorithm is the modified Confusion Assessment Method for the Emergency Department, a feasible approach based on the original short version of the CAM. The scale requires a maximum of one minute to evaluate attention and 3 to 5 min to complete the whole instrument. The sensitivity and specificity reported in the original

study was only for the informal delirium assessment. The authors concluded that the study indicated for the need for a standardized, formal delirium screening and assessment instrument in the ED [22].

3.3. Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)

The CAM-ICU [7] is a modified version of the CAM for use in the ICU and/or in critically ill patients. Overall, it considers the same CAM features of delirium evaluation. The main difference between the scales is that the CAM requires clinical judgment to assess for all four features, while the CAM-ICU encompasses brief neuropsychiatric assessments to determine inattention (Feature (2)) and disorganized thinking (Feature (3)). Additionally, the CAM-ICU is easier and faster to apply (less than 2 min to complete), making it ideal for the busy ED environment and attending to the critical status of the patient [8]. The sensitivities were 72.0% and 68.0% in the Emergency physicians and Research assistants, respectively. The CAM-ICU's specificity was 98.6% [27]. However, as a drawback, while the CAM-ICU attempts to evaluate disturbances in attention and cognition, it fails to capture their fluctuating nature since the evaluation is done at one point in time.

3.4. Delirium Triage Screen (DTS)

The DTS [30] was designed for application in a very brief length of time (less than 20 s) so that it could be easily integrated into the clinical environment. It consists of two components: level of be ruled out in this case with no need for additional delirium testing. Nevertheless, since the DTS is 55% specific, other confirmatory evaluations are warranted (specifically using the CAM or bCAM) to rule in delirium [30]. Of note, the bCAM (as well as the DTS) are part of the Geriatric Emergency Department Guidelines.

3.5. Brief Confusion Assessment Method (bCAM)

The bCAM [31] is an adaptation from the full CAM and it comprises four questions that have been widely validated to make diagnosis of delirium: two fundamental features (acute onset and fluctuating course, and inattention), and two secondary features. The bCAM takes less than 2 min to perform and it was designed to improve CAM sensitivity and enhance its brevity [30] with the addition of an inattention task in which it is required to the patient to recite the months backwards from December to July.

3.6. Neelon and Champagne Confusion Scale (NEECHAM)

The NEECHAM Confusion Scale [32] is an observational scale with nine interactive items, divided in three subscales: processing, behavior and physiological control. A score of 30 indicates normal function and 0 severe confusion, with a range of 25–26 as "at risk for confusion". It was developed for use as a rapid bedside assessment by nurses and has been applied on several samples and settings to detect delirium in the early stages, follow-up on progress and identify regression of a confusional state [37,38]. This instrument shows sensitivity and specificity values ranging from 30% to 95% and 78% to 92%, respectively. An additional advantage of the NEECHAM is its sensitivity to both the hyperactive and hypoactive variants of delirium [39].

3.7. Richmond Agitation Sedation Scale (RASS)

The RASS [34] is a measure of the level of arousal, being commonly used in clinical practice and research setting to assess for depth of sedation. Nonetheless, it has been incorporated into several delirium assessments, such as the bCAM and the CAM-ICU, to assess for level of consciousness [36]. It has a 10 level scale ranging from +4 ("combative) to −5 ("unrousable") that can be briefly rated. The RASS takes less than one minute to complete and can be assessed by simply observing the patient during routine interactions and does not require additional cognitive testing [10]. This tool has been demonstrated to have excellent inter rater reliability and excellent validity when compared, for instance, to other sedation scales [40]. The diagnostic accuracy of the RASS for delirium in older patients, when applied by a physician, had a sensitivity of 82% (71.4%–92.6%) and a specificity of 85.1% (81.4%–88.8%) for a RASS other than 0, and for a RASS > +1 or < −1 had a sensitivity of 16.0% (5.8%–25.2%) and a specificity of 99.7% (99.2%–100%). Similar results were obtained when the RASS was applied by the research assistant [10].

4. Concluding Remarks

This review provides an update on delirium diagnostic and screening tools for use in the ED. Here, seven different scales were identified for evaluation/assessment of delirium in the ED setting. Comparing with previous reviews of literature [6] some important differences should be noted, namely that prior work identified a different group of scales. Of these, four overlap with the ones here comprised: CAM, CAM-ICU, CAM-ED, and NEECHAM. Here, we further identified the mCAM-ED, DTS, bCAM and RASS, while the previous authors consider the Diagnostic and Statistical Manual criteria

(DSM) and the Delirium Rating Scale (DRS) in their analysis. Other differences and/or considerations are finally also warranted. First, here we do not consider that the original study by Lewis et al. (1995) [9] deems a formal change of designation to CAM-ED. Second, the recent work of Grossman et al. (2014) [22] has been included, which formally addresses the question of the CAM adaptation for the ED (termed mCAM-ED); thus, considering it its own independent instrument, although the study did not have sufficient power to calculate sensitivity and specificity. Finally, of note, here the OBS scale was not included if considering that the studies reporting on it were not conducted in the ED.

It is relevant to note the advances in the field since 2014. A total of three new delirium screening scales for the ED are indicated: DTS, bCAM and mCAM-ED, if considering the DTS as the bCAM as separate instruments. In addition, an important breakthrough in the field is of particular note with the formal validation of the CAM-ICU for the ED. The CAM-ICU is highly specific in older ED patients, regardless of administration by research assistants or emergency physicians [7]. However, this is true at the cost of a moderate sensitivity. The CAM-ICU authors addressed this issue in two separate but related studies [7,36]. On a first approach, the importance of a brief and easy-to-use delirium assessment tool appropriate for the fast-paced ED environment was considered with the validation of the CAM-ICU; and, within this up-to-date review, it is important to note that only the study of Sufolletto et al. (2013) did address this topic [27]. A brief and novel two-step approach for delirium surveillance was later defined with the DTS and the bCAM. A negative DTS essentially rules-out delirium and reduces the number of formal delirium assessments needed, increasing screening efficiency; thereafter, following with the bCAM, a balance between brevity and diagnostic accuracy is achieved, and it is an effective rule-in delirium assessment. Third, we included in this review the RASS scale. Although this instrument is not a delirium screening tool per se, the RASS scale has been demonstrated to have a very good specificity for detecting delirium in patients older than 65 years old, with a cut-off >+1 or <−1. The scale may be a reasonable alternative to monitor for delirium in the ED, especially when ED health care providers are faced with significant time constraints [36].

As highlighted in other general reviews about delirium scales [41], only the instruments which are used for diagnosis (i.e., CAM and CAM-ICU) and that are based on various Diagnostic and Statistical Manual criteria, have good to excellent reliability and fair to good validity. In this sense, only the studies of Han and colleagues [4,7,30,36] address the main psychometric characteristics of delirium in the ED, based on the CAM attributes, and explored its sensitivity and specificity. From this frame, it is here proposed that delirium research should evolve to focus in novel attention tests and testing their performance

against CAM-ICU and DTS/bCAM approach(es), in order to be feasible, useful and of needed sensitivity/specificity in the particular setting of the fast-paced emergency care units.

Another problem that should be addressed and clarified in the future is the distinction between the acute setting of delirium, secondary to medical illness, and the (expected) cognitive decline in ageing, irrespective of the underlying medical condition. That is, the current tools may not properly distinguish between an acute cognitive "failure" (delirium, which is considered to be "organic") from one that is sustained (underlined by reasons other than delirium, in which ageing itself plays a relevant role), albeit both may co-exist.

Cognitive disturbances are a "part and/or parcel" of delirium, and thus cannot be disregarded [41]. Perhaps due to this, and also because the onset itself of delirium and that which triggers it is not completely yet clarified, many of the instruments which have been primarily designed to assess disturbances in cognitive functions have been also been used for screening for delirium [41]. Nonetheless, as pointed by Grover et al. (2012) [41], particularly some of the earlier instruments which were used to assess the severity and phenomenology of delirium did not assess the cognitive functions comprehensively; that is, these are useful as supplementary tools for assessment of cognitive functions in patients of delirium. These include the MMSE [42], Cognitive test for Delirium (CTD) [43], Clock Drawing Test [44], Digit Span Test [45], Vigilance "A" test [44], Mental State Questionnaire (MSQ) [46,47] and the Short Portable Mental Status Questionnaire [48]. Here it is argued that delirium diagnosis should comprise a two-step approach: (i) cognitive screening with a rapid assessment tool, which should be overall acceptable for different populations and literacy levels; and (ii) delirium diagnosis/confirmation with a delirium tool. Delirium is more common in the elderly, some of whom also suffer from dementia; hence, it is also important to have an understanding of baseline cognitive functions of patients before considering the cognitive disturbances as part of the delirium. In fact, differentiating dementia from delirium is a challenge for health professionals. Among older/elder individuals, up to two-thirds of cases of delirium are superimposed with dementia, and delirium may lead to severe cognitive impairment, and many patients who have experienced delirium are at greater risk to develop dementia [23,49]. More so, patients with dementia present characteristics very similar to the symptoms of delirium profile [50]. On this, besides cognitive scales that can help to discriminate these conditions in the moment of screening and diagnosis, electroencephalography (EEG) already showed a great specificity and adequate sensitivity [51]. Caregivers' information or informant-based screening tools are also crucial to determine if there has been an acute decline (a feature of delirium),

but also to verify if there has also been a much more prolonged decline in time (characteristic of dementia). This kind of instruments/information, such as the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE; [52]) can be less likely to be influenced by the acute condition of the patient and can complement the other performance tools when used in combination.

In conclusion, besides a wide consensus on the importance of recognizing delirium in the ED, there are still few (albeit strong) attempts to clarify this important issue. Among the instruments considered, the CAM-ICU is the most widely used, although its validation is in single center studies. Despite its limitations, it surfaces as the most favorable instrument for use in critical care because of its accuracy, brevity, and ease of use by clinical and lay interviewers. In the future, research in a global approach of evaluation of actual and past cognitive changes should be considered and validation of these delirium assessments in other centers will be critical to determine which delirium assessment would be the most accurate for the ED settings. The balance between a comprehensive evaluation and the necessary brevity of the screening must, however, remain in the forefront.

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CHAPTER IV

The Confusion Assessment Method for Intensive Care Unit: A Large Cohort Validation Study in the Emergency Department of a Tertiary Hospital

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The Confusion Assessment Method for Intensive Care Unit: A Large Cohort Validation Study in the Emergency Department of a Tertiary Hospital

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Resumo:

Introdução: A escala Confusion Assessment Method for Intensive Care Unit (CAM-ICU) apresenta um grande potencial de aplicação no Serviço de Urgência (SU). No entanto, existem ainda incertezas relativas a sua acurácia e fiabilidade, requerendo estudos com maiores coortes. Numa das maiores e mais heterogéneas coortes conhecidas ate o momento, aqui o objetivo foi validar e explorar a aplicabilidade da CAM-ICU (versão Português Europeu) como ferramenta de rastreio e diagnostico de delirium no SU de um hospital terciário.

Métodos: Os dados foram colhidos aleatoriamente e prospectivamente numa amostra de conveniência em doentes adultos admitidos no SU do Hospital de Braga. O delirium foi primeiramente avaliado usando a CAM-ICU. Para a

validação, o padrão de referência foi a avaliação psiquiátrica, efetuada em intervalo de 3 horas da CAM-ICU, por psiquiatra oculto ao seu resultado, usando os critérios de diagnósticos da DSM-5, sem interferência nos procedimentos do SU relativa a operacionalização das avaliações psiquiátricas.

Resultados: Apos aplicar os critérios de exclusão/inclusão, dos 592 doentes avaliados, 19,8% foram diagnosticados com delirium usando a CAM-ICU. O padrão de referência foi aplicado a 81 doentes. A CAM-ICU apresentou uma sensibilidade de 95,2% (IC 95% = 74,1 a 99,8) e especificidade de 88,3% (IC 95% = 76,8 a 94,8). A CAM-ICU mostrou uma acurácia de 90,1% em relação ao padrão de referência.

Conclusão: A CAM-ICU (versão Portuguesa) é um instrumento pratico, valido e fiável para a avaliação de *delirium* em ambiente real de SU, mostrando uma sensibilidade, especificidade e acurácia para o diagnostico de *delirium*.

Palavras-chave: Delírio/diagnóstico; Índice de Gravidade de Doença; Serviço de Urgência Hospitalar; Unidades de Cuidados Intensivos

Abstract:

Introduction: The Confusion Assessment Method for Intensive Care Unit (CAM-ICU) is of great potential value in the emergency department (ED). However, there is still uncertainty about its diagnostic accuracy and reliability, with studies warranting larger cohorts. In one of the largest and most heterogeneous cohorts considered to date, the aim was to validate and explore the applicability of the CAM-ICU (European Portuguese) as a delirium screening and diagnostic tool in the ED setting of a main hospital referral centre.

Methods: Data were randomly and prospectively recorded in a convenience sample of patients with 18 years or older admitted to the ED of Hospital de Braga (Braga, Portugal). Delirium status was primarily assessed using the CAM-ICU. For the validation aspect, the reference standard was a psychiatric evaluation, conducted within 3 hours of the CAM-ICU by a psychiatrist blind to the finding, using the DSM-5 diagnostic criteria, without external interference on the regular proceedings in the ED on the timing, number and operationalization of psychiatric evaluations in the setting.

Results: After exclusion/inclusion criteria, of the 592 patients evaluated, 19.8% were diagnosed with delirium using the CAM-ICU. The reference standard was applied to 81 patients. The CAM-ICU presented a sensitivity of 95.2% (95% CI= 74.1 to 99.8) and specificity of 88.3% (95% CI= 76.8 to 94.8). CAM-ICU showed an accuracy of 90.1% with the reference standard.

Conclusion: The CAM-ICU (Portuguese version) is practical, valid and reliable instrument for the assessment of delirium in the real setting of an ED showing sensibility, specificity and accuracy for delirium diagnosis.

Keywords: Delirium/diagnosis; Emergency Service, Hospital; Intensive Care Units; Severity of Illness Index.

Introduction

Delirium is a common neurobehavioral syndrome considered to be caused by a dysregulation of baseline neuronal activity secondary to systemic disturbances.[1] In the hospital setting, delirium is a risk factor for clinical complications, a longer length of stay and discharge to a post-acute nursing facility.[2] Even with respect to long-term outcomes there is evidence that delirium episodes are associated with poorer outcome, independently of confounders such as age, sex, comorbid illness or illness severity, and baseline dementia.[3] It is well recognized that the first step in delirium management, in any hospital setting, is to perform a timely and accurate diagnosis, preferably via the use of a brief (validated) instrument that assesses features in the Confusion Assessment Method algorithm.[2,4] The systematic assessment of delirium may, nevertheless, be rendered difficult in the Emergency Department (ED) due to the intrinsic characteristics of the setting: acute patients and time constraints. Thus, for the ED, the few studies available indicate that health care providers may miss delirium up to approximately 75% of the time,[5-7] which may hinder a translation into appropriate (early) treatment measures of delirium.[5,6]

For the ED environment, a total of 7 different scales have been identified for delirium screening.[5] Of these, The Confusion Assessment Method for Intensive Care Unit (CAM-ICU) is the most widely used.[5,6] Overall, the CAM-ICU has shown a good profile of specificity and sensitivity, having been validated across different hospital settings.[8-13] Concerning the ED setting there are few studies; however, Han *et al* (2014) validated the CAM-ICU in the ED in a cohort of 406 older (>65 years) patients. The study indicated a CAM-ICU sensitivity of 72.0% (95% confidence interval [CI] = 58.3% to 82.5%) and 68.0% (95% CI = 54.2% to 79.2%) in the emergency physician and in the research assistants' application of the scale, respectively, and a specificity of 98.6% (95% CI = 96.8% to 99.4%) for both raters.[7] In Europe, so far, the only study that directly addressed the process of validation of the CAM-ICU for delirium in the ED setting, from Van de Meeberg *et al*, reported a sensitivity of 100%, a specificity was 98%, and a positive predictive value of 92%, and negative predictive value was 100%.14 In another study from Holland, Lucke *et al* applied the CAM-ICU in a large cohort of ED patients, and founded a low prevalence of delirium, suggesting a low performance. However, it was not a study of the validation of the CAM-ICU in the ED.[15]

To our knowledge, no other groups have addressed the performance of the CAM-ICU in the ED, particularly outside the United States. In fact, a recent review indicates that the validation data of the CAM developed specifically for the ED setting is limited.[16] Thus, despite the relevant work on the application of the CAM-ICU in critically ill, intensive care unit and older patients,[7,8,11-13] uncertainty about

its diagnostic accuracy and reliability remains,[7] with an identified need for continued assessment across ED settings and in large(r) cohorts.[5]

Here, in the ED of a main hospital referral centre, across its emergency units (allocation to these specialized units is based on patients' screening and severity), the aim was two-fold: (i) to compare the results of the CAM-ICU on the identification of delirium *versus* the 'gold standard' DSM-5, and (ii) to address for the applicability of the CAM-ICU European Portuguese version, as applied by researchers (senior medical students) and medical professionals (emergency internists), trained for its application, "in lieu" of the DSM-5.

Methods

CHARACTERIZATION OF THE EMERGENCY DEPARTMENT

The study was conducted at the ED of Hospital de Braga (Braga, Portugal), a University of Minho (Braga, Portugal) affiliated hospital with 705-beds, which serves a population of 1 200 000 as a tertiary referral centre. The ED at the Hospital de Braga has an annual census of approximately 175 000 visits, and it comprises two ED clinical decision units, the EDCDU1 and the EDCDU2, an ED physician office (EDPHOF) and an ED intermediate care unit (EDIMCU). These units are rooms properly organized with priority hierarchies based on patients' screening and severity. All the units are physically connected to the ED, sharing medical and nursing staff.

For the ED patients (all age ranges), the EDCDUs provide an alternative to discharge or hospital inpatient admission; patients may benefit from an extended observation period, generally less than 24 hours. Patients screened on admission with the Yellow or the Orange criteria of the Manchester triage, 17 or who need to stay in the supine position in a stretcher, are referred to the EDCDU1 and the EDCDU2, respectively. The EDPHOF unit attends to problems related to patients' health with low severity degree; where, any patient screened to the EDPHOF may be forwarded to other ED units in case of worsening health status and if this referral is justified. The EDIMCU is a 9-bed unit that receives patients from multiple intra- and inter-hospital origins, including from the ED, surgical and medical wards (as a step-up unit), ICU (as a step-down unit), recovery operatory room, and other hospitals (without intermediate and/or intensive care units). The criteria for admission to the EDIMCU follows the Guidelines on Admission and Discharge for Adult Intermediate Care Units of the Society of the Critical Medicine.[18]

STUDY POPULATION AND DESIGN

In order to obtain an approximate sample to the reality of the ED at Hospital de Braga, across time, data were randomly and prospectively recorded, in a convenience sample,across [3] separate collection periods (June 2014 to November 2014; July 2015; and, April 2016 to July 2016), across the ED units (EDCDU1 and 2, EDIMCU and EDPHOF). Winter season (December to March) was not considered due to the ED overcrowding (mainly respiratory illnesses in older adults and chronic patients), and the potential overextension of the ED waiting period, or length of stay, that can characterize the Department in that time of year [a phenomenon termed "exit block" (or access block).[19]

The study inclusion criteria included patients aged 18 years or older, admitted to the ED, whenever members of the study research team were present. Patients were excluded if: (i) obstetric and pediatric population; (ii) ambulatory patients in their full range of movements and autonomous who refer directly to the ED; or, (iii) unviable to assess for delirium using the CAM-ICU20 at any time during the initial screening procedure, including clinical evaluation refusal by the patient, inability to follow simple commands before acute illness onset, language communication barriers, advanced dementia previously diagnosed, or other diagnosed neuropsychiatric disorder, and coma. The exclusion criteria used are in accordance with previous similar studies.[8,21] Patients who had been evaluated using the CAM-ICU in prior ED admissions, or that were evaluated outside the formal study periods of assessment for the purpose of this work, were also excluded due to impossibility to control any methodological or selection bias. The sample size estimated to determine de validity of the CAM-ICU was based on the subject to item ratio. A subject to item of 10 was fixed as the minimum, which makes it necessary to have a minimum sample of 70 patients enrolled considering 7 items associated with CAM-ICU: Feature 1, Feature 2, Feature 3, Feature 4 (which contains 4 questions to evaluate the disorganized thinking)[22]

Before the start of data collection, all researchers (senior medical students) and medical professionals (emergency internists), who participated in delirium assessment using the CAM-ICU, underwent a training period coordinated by two staff members as part of the hospital Quality Assurance Program. Training materials were provided by Vanderbilt University including training manuals, didactic lectures, demonstrations and direct practice of the assessment tools in patient scenarios.[20]

The Ethical Committee at Hospital de Braga approved the study protocol and waived informed consent. The study was non-interventional; therapies with regard to the clinical diagnosis, delirium and sedation state were left to the discretion of the attending physician.

MEASUREMENTS

Delirium status was assessed using CAM-ICU20 following the same methodology reported by Han *et al*[7],[23] and Mariz *et al*.[21] The CAM-ICU takes less than 2 minutes to complete and reports on: i) acute onset of mental status changes or a fluctuating course, ii) inattention, iii) disorganized thinking, and iv) altered level of consciousness.[8,20] The Richmond Agitation and Sedation Scale (RASS) was used to categorize the psychomotor subtype of delirium (RASS score between: +1 and +4, hyperactive delirium; 0 and -3, hypoactive delirium).[20,24] Depending on resident psychiatrists' availability, within a 3-hour time period of the CAM-ICU assessment by the researcher/medical professional, and if the patient had not yet been discharged from the ED, delirium was assessed by the resident psychiatrist using the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as the gold standard for delirium status diagnosis.[4] This involved an inclusive interpretation of Criteria A and D, as indicated by the European Delirium Association and the American Delirium Association.[25] The psychiatrists involved in the study have a permanent presence at ED, sharing the patients' management in the same setting as the physicians in the frontline of the ED, but were blind to the CAM-ICU result. Patients were assessed no more than once by each method and, if evaluated by both methods, these were conducted within a 3-hour timeframe.

Patient data included: age, gender, admission type (emergency department, operating room, wards, intensive care unit, inter-hospital transfer), location in the ED, and diagnostic groups (cardiovascular, drug toxicity/ withdrawal, gastrointestinal, genitourinary, neurologic, haemato-oncologic, pulmonary, trauma/ musculoskeletal and other). The systemic inflammatory response syndrome (SIRS) criteria (two or more of the following criteria: heart rate > 90 beats/min; body temperature < 36 or > 38°C; respiratory rate > 20 breaths/min; white blood cell count < 4x109 or > 12x109 cells/L [23]) was used as a surrogate for severity of illness. Data were collected from the Clinical Process through the Glintt® computer system which only the researcher responsible for the project had access.

STATISTICAL ANALYSIS

All statistical analyses were conducted using SPSS statistics version 23.0. Measures of central tendency and dispersion for continuous variables were reported as medians and standard deviation (SD). Categorical variables were reported as absolute numbers and proportions. Criterion validity was determined by comparing the CAM-ICU raters to the delirium expert rating by using the DSM-5 criterion as the reference standard. To determine validity a 2 x 2 table was created comparing the reference

standard ratings with the CAM-ICU ratings included the number of true positives (TP), false positives (FP), false negatives (FN), and true negatives (TN). Sensitivity= TP/(TP+FN); specificity=TN/(FP+TN); accuracy=(TP+TN)/(TP+FP+FN+TN); likelihood ratio= sensitivity/(1-specificity); positive predictive value (PPV) and negative predictive value (NPV). Ninety-five percent confidence intervals (CI) for these test characteristics were calculated by using "*VassarStats: Website for Statistical Computation*" (http://vassarstats.net). Exact chi-square testes and ANOVA analysis were performed as appropriate to determine if baseline features differed between 'Delirium' and 'No Delirium' groups. Prevalence of delirium in the ED of Hospital de Braga was determined. Agreement between CAM-ICU/DSM-5 diagnosis of delirium was calculated with the kappa statistic and the McNemar's test.

Results

A total of 768 patients were screened in the time periods referred; of these, all 592 patients that met the inclusion criteria (study sample) were evaluated using the CAM-ICU and, of these, 81 (13.7%) were further evaluated by the resident psychiatrist on duty (blind to the CAM-ICU result) following the DSM-5 criteria (Fig. 1).

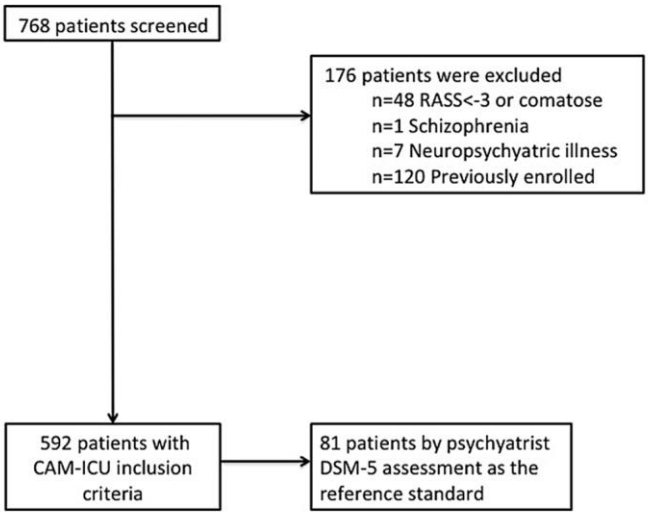


Figure 1 Flow chart of the study sample selection.

Baseline characteristics of the study cohort are presented in Table 1. The median age of the study sample was 65.74 years old (± 18.68), 61.3% (n = 363) were aged 65 years or more, and 263 (44.4%) were female. The distribution of patients by emergency units was: 35.5% (n = 210) EDCDU1, 33.6% (n = 199) EDCDU2, 27.4% (n =162) EDIMCU and 3.5% (n = 21) EDPHOF. Characteristics of the CAM-ICU evaluation cohort by the ED physicians versus the psychiatric evaluation cohort are presented in Table

2. There were no significant differences between the psychiatric evaluation and the ED physician's evaluation, besides more patients from intra-hospital transfer in the former (32.1% *vs* 20.9%; p = 0.021).

Table 1 Patient characteristics stratified by delirium status assessed using CAM-ICU.

	Delirium	**No delirium**	**p-value**
Patients, n (% total) [a]	117 (19.8%)	475 (80.2%)	p <0.001
Characteristic			
Mean age, years (SD)	76.0 (±14.0)	63.2 (±18.7)	p <0.001
Female, n (% group)	71 (60.7%)	192 (40.4%)	
SIRS criteria, %	29 (24.8%)	81 (17.1%)	p = 0.049
Emergency Department Units, n (%group, %emergency department)			p = 0.072
EDCDU1	39 (33.3%; 18.6%)	171 (36.0%; 81.4%)	
EDCDU2	32 (27.4%; 16.1)	167 (35.2%; 83.9%)	
EDIMCU	43 (36.8%; 26.5%)	119 (25.1%; 73.5%)	
EDPHOF	3 (2.6%; 14.3%)	18 (3.8%; 85.7%)	
Admission type, n (%group, %origin) [b]			p = 0.012
Home	65 (55.6%; 16.3%)	335 (70.5%; 83.8%)	
Elderly home	5 (4.3%; 35.7%)	9 (1.9%; 64.3%)	
Intra-hospital transfer	37 (31.6%; 27.8%)	96 (20.2%; 72.2%)	
Inter-hospital transfer	10 (8.5%; 22.2%)	35 (7.4%; 77.8%)	
Emergency physician diagnosis by organ n (%group, %diagnostic)			p = 0.172
Cardiovascular	10 (8.5%; 11.6%)	76 (16.0%); 88.4%)	
Drug toxicity/withdrawal	4 (3.4%; 28.6%)	10 (2.1%; 71.4%)	
Gastrointestinal	17 (14.5%; 17.3%)	81 (17.1%; 82.7%)	
Genitourinary	16 (13.7%; 19.0%)	68 (13.5%; 81.0%)	
Neurologic	14 (12.0%; 21.9%)	50 (10.5%; 78.1%)	
Hemato-oncologic	3 (2.6%; 16.7%)	15 (3.2%; 83.3%)	
Pulmonary	23 (19.7%; 26.4%)	64 (13.5%; 73.6%)	
Trauma/musculoskeletal	5 (4.3%; 11.4%)	39 (8.2%; 88.6%)	
Other	25 (21.4%; 25.8%)	72 (15.2%; 74.2%)	

[a] Of the n=768 patients enrolled, n=176 were excluded due to schizophrenia, RASS<-3 or comatose, neuropsychiatry illness or previously enrolled patients (CAM-ICU not conducted). SIRS systemic inflammatory response syndrome.

[b] Significant differences between Home and Intra-hospital transfer (p=0.019). ED emergency department; EDCDU1 emergency department acute unity 1 - yellow Manchester screening; EDCDU2 emergency department acute unity 2 – orange Manchester screening; EDIMCU emergency department intermediate care units; EDPHOF- emergency department physician office; CAM-ICU confusion assessment method for intensive care unit; SD standard deviation.

Table 2 Patient characteristics stratified by evaluation.

	Delirium Psychiatrist evaluation cohort	Emergency physician evaluation cohort	p-value
Patients, n (% total) [a]	81 (13.7%)	511 (86.3%)	
Characteristic			
Mean age, years (SD)	67.64 (±18.1)	65.43 (±18.6)	*p = 0.276*
Female, n (% group)	44 (54.3%)	192 (42,9%)	*p* = 0.054
SIRS criteria, %	19 (23.5%)	91 (17.8%)	*p = 0.225*
Emergency Department Units, n (%group)			
EDCDU1	99 (35.8%)	181 (35.4%)	*p* = 0.947
EDCDU2	22 (27.2%)	177 (34.6%)	*p* = 0.186
EDIMCU	28 (34.6%)	134 (26.2%)	*p* = 0.118
EDPHOF	2 (2.5%)	19 (3.7%)	*p* = 0.573
Admission type, n (%group)			
Home	48 (59.3%)	352 (58.9%)	*p* = 0.086
Elderly home	2 (2,5%)	12 (2.3%)	*p* = 0.947
Intra-hospital transfer	26 (32.1%)	107 (20.9%)	*p* = 0.021
Inter-hospital transfer	5 (6.2%)	40 (7.8%)	*p* = 0.602
Emergency physician diagnosis by organ n (%group)			
Cardiovascular	15 (18.5%)	71 (13.9%)	*p* = 0273
Drug toxicity/withdrawal	4 (4.9%)	10 (2.0%)	*p* = 0.101
Gastrointestinal	9 (11.1%)	89 (17.4%)	*p* = 0.172
Genitourinary	10 (12.3%)	74 (14.5%)	*p* = 0.156
Neurologic	7 (8.6%)	57 (11.2%)	*p* = 0.499
Hemato-oncologic	4 (4.9%)	45 (2.7%)	*p* = 0.285
Pulmonary	13 (16%)	74 (14.5%)	*p* = 0.711
Trauma/musculoskeletal	2 (2.5%)	42 (8.2%)	*p* = 0.067
Other	217(21%)	80 (15.7%)	*p* = 0.229

[a]Of the n=768 patients enrolled, n=176 were excluded due to schizophrenia, RASS<-3 or comatose, neuropsychiatry illness or previously enrolled patients (CAM-ICU not conducted). SIRS systemic inflammatory response syndrome.

ED emergency department; EDCDU1 emergency department acute unity 1 - yellow Manchester screening; EDCDU2 emergency department acute unity 2 – orange Manchester screening; EDIMCU emergency department intermediate care units; EDPHOF- emergency department physician office; CAM-ICU confusion assessment method for intensive care unit; SD standard deviation.

Using the CAM-ICU, delirium was observed in 17.6% (90/511) (ED physician evaluation); while, using the standard evaluation technique DSM-5, 25.9% (21/81) delirium cases were diagnosed (psychiatric evaluation). Characteristics of the "Delirium" patients are presented in Table 3; these were significantly older compared to "No Delirium" (mean 71.0 *vs* 66.5, p <0.001) and presented higher percentage conforming to the SIRS criteria (38.1% *vs* 18.3%, p = 0.034). Most patients were alert and calm at evaluation time (RASS = 0; 68.1% via CAM-ICU, 70.4% via DSM-5); most of those assessed with delirium were hypoactive (79.5% via CAM-ICU; 71.4% via DSM-5). One false negative was observed; at the moment of CAM-ICU assessment, the patient was at his mental status baseline (RASS=0) and there was no evidence of a fluctuating course of mental status.

Table 3 Patient characteristics stratified by delirium status assessed using both the CAM-ICU and the DSM-5 by psychiatrist assessment.

	Delirium	**No delirium**	**p-value**
Patients, n (% total)	21 (25.9%)	60 (74.1%)	p <0.001
Characteristic			
Mean age, years (SD)	71.0(±15.7)	66.5 (±18.9)	p <0.001
Female, n (% group)	10 (47.6%)	34 (56.7%)	p = 0.585
SIRS criteria, %	8 (38.1%)	11 (18.3%)	*p = 0.034*
Emergency Department Units, n (%group, %emergency department)			*p = 0.084*
EDCDU1	6 (28.6%)	23 (38.3%)	
EDCDU2	2 (9.5%)	20 (33.3%)	
EDIMCU	12 (61.9%)	15 (25.0%)	
EDPHOF	-	2 (3.3%)	
Admission type, n (%group, %origin)			*p = 0.032*
Home	7 (33.3%)	41 (68.3%)	
Elderly home	1 (4.8%)	1 (1.7%)	
Intra-hospital transfer	10 (47.6%)	16 (26.7%)	
Inter-hospital transfer	3 (14.3%)	2 (3.3%)	
Emergency physician diagnosis by organ n (%group, %diagnostic)			*p = 0.144*
Cardiovascular	1 (4.8%)	14 (23.3%)	
Drug toxicity/withdrawal	1 (4.8%)	3 (5.0%)	
Gastrointestinal	2 (9.5%)	7 (11.7%)	
Genitourinary	3 (14.3%)	7 (11.7%)	
Neurologic	4 (19.0%)	3 (5.0%)	
Hemato-oncologic	-	4 (6.7%)	
Pulmonary	3 (14.3%)	10 (16.7%)	
Trauma/musculoskeletal	1 (4.8%)	1 (1.7%)	
Other	6 (28.6%)	11 (18.3%)	

The CAM-ICU identified 20 of the 21 delirious patients identified by the DSM-5 and showed an overall sensitivity of 95.2% (95% CI= 74.1 to 99.8) and specificity of 88.3% (95% CI= 76.8 to 94.8). The negative likelihood ratio (LR-) was 0.05 (95% CI= 0.01 to 0.37). The positive likelihood ratio (LR+) was 8.16 (95% CI= 4.04 to 16.48) (Tables 4 and 5).

Table 4 Diagnostic performance of the CAM-ICU.

Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95%CI)	LR- (95% CI)	PPV (95% CI)	NPV (95% CI)
95.2%	88.3%	8.16	0.05	74.1%	*98.1%*
(74.1-99.8)	(76.8-94.8)	(4.04-16.48)	(0.01-0.37)	(53.4-88.1)	*(88.8-99.9)*

LR+ positive likelihood ratio; LR- negative likelihood ratio; PPV positive predictive value; NPV negative predictive value; CI confidence interval; CAM-ICU Confusion Assessment Method for Intensive Care Unit

Table 5 A comparison of the CAM-ICU and the DSM-5.

		Delirium	No delirium	Total
CAM-ICU	DELIRIUM	20	7	27
	No delirium	1	53	54
	Total	21	60	81

Kappa coefficient: 0.77, $p<0.001$; McNemar Test $p=0.070$. CAM-ICU Confusion Assessment Method for Intensive Care Unit; DSM-V Diagnostic and Statistical Manual of Mental Disorders.

Discussion

A psychiatric evaluation of a fluctuating case in an ED is a high constrain depending on time and immediate psychiatric staff availability, with time being of priority in delirium treatment. The present study was carried out in the ED of a central district hospital, across multiple collection points, assessing for a large cohort of patients. The study corroborates for the easy-of-use of the scale and its feasibility and practicality in the ED setting. The scale incorporates objective assessments, allowing to remove any possible subjectivity from delirium assessment and rendering it easier to use by eventually less experienced users.

The results indicate that the CAM-ICU has high levels of sensitivity (95.2%: 95% CI= 74.1 to 99.8) and specificity (88.3%: 95% CI= 76.8 to 94.8), suggesting that when the CAM-ICU is positive (in the ED setting) any relevant treatment for this condition may be initiated. A common feature of every published research work on CAM-ICU is its high specificity. The routinely use of delirium screening and diagnostics tools can increase the detection rate of cases. Ely *et al* (2001) carried out the first validation study of the CAM-ICU in an intensive care unit (ICU) in critically ill patients in a study sample of 31 patients.[8] The study showed a high specificity (95% to 100%) and sensitivity (89% to 93%) and an

excellent interrater correlation. The same authors published a second study enrolling 111 patients on mechanical ventilation that confirmed the high interrater correlation (kappa coefficient: 0.99, 95% CI: 0.92 – 0.99), and the high sensitivity (93% to 100%) and specificity (98% to 100%) of the scale.[9] Tobar *et al* (2010) validated the Spanish CAM-ICU version in 29 critical patients, also undergoing mechanical ventilation, obtaining a sensitivity between 80% to 83% and a specificity of 96%.[10] Flores *et al*, (2011) validated the CAM-ICU in a mixed population of critically ill patients in four ICUs in Brazil, enrolling a total of 119 patients, and showed an overall sensitivity of 72.5% (95% CI: 55.9% – 84.9%) and specificity of 96.2% (95% CI: 88.5% – 99%).[11]

Still, the present study differs in some respects from other works. Here, at 88.3%, the calculated specificity was not as high for the CAM-ICU as others have published (varying from 93% to 100%). This difference does not seem to be related to the implementation of CAM-ICU using the European Portuguese language as other authors have applied Spanish and Portuguese (Brazil) and translations of the CAM-ICU and have obtained high specificities.[10,11,14] The most likely explanation relates with the patient's characteristics. Here, the study was carried out with a high spectrum of patients with different characteristics, including range in ages, emergency physician diagnosis, admission type and disease severity. In contrast, many of the previous studies were done using more homogeneous cohorts either in terms of age and less critical conditions, 7 or in well-defined diagnosis groups such as medical oncology and patients with acute stroke.[12,13] Thus, the sensitivity and specificity differences showed in different CAM-ICU validation works may be related to the patients' characteristics, namely age and illness severity, warranting continued work in the area. Nonetheless, it also of note that a cohort's heterogeneity may not necessarily explain relatively low specificities. The CAM-ICU's specificity may also be diminished in patients with dementia[7] or, also of consideration, can also be explained by random chance. Here, the sensitivity obtained for the CAM-ICU presented a higher value than the values presented in other studies, which may be related with the (high) severity of patients in the cohort.

There are other influences to be noted, regarding ED organization and structure. In particular, our ED system is very based on Clinical Decision Units (CDU), that overall could be partially compared with the Observation Units in the US, although CDU are fully integrated in the ED. More so, our ED is an open system, absorbing a very substantial proportion of non-urgent situations, which for a multitude of reasons are not managed in the primary care system. It is estimated that approximately 25% of the attendees at hospital emergency units do not need immediate care.26 This number can be higher in central district hospitals. Accordingly, at the ED of Hospital de Braga, following the Manchester Triage

System classification, an average of 35% of patients were green coded in 2017 (internal hospital data, unpublished), mainly in the EDPHOF. For that reason, we chose not to include patients from the EDPHOF, as these patients are mainly low priority, non-urgent patients, who should have been attended in their GPs.

LIMITATIONS

The study has limitations that are of note. Throughout the data collection time periods different researchers/medical professionals applied the CAM-ICU. Albeit all receiving the same procedural training this may potentially have influenced results. Nonetheless, the tool is simple and easily applied, and several studies have indicated for an excellent interrater correlation in the application of the CAM-ICU. In this regard, another possible limitation was that only research personnel and clinicians administered the CAM-ICU (the scale was not applied by support staff to the ED, technical staff or nurses); which may bias possibly toward higher performances of the CAM-ICU. Still, the researchers were senior medical students, which may add value to the hypothesis that even less experienced health personal may, when properly trained, also aptly apply the tool.

Another limitation, a selection bias is of note given that a convenience sample was enrolled for the confirmatory psychiatry evaluation (those present in the ED at the time) due to the difficulty of psychiatrist's availability by limitations of staff. Albeit the psychiatrist having no influence on the selection of patients, the difference of CAM-ICU positive patients between the group who received the psychiatrist evaluation and the group who did not (26% vs 33%, respectively) may point out that psychiatrists may have inadvertently selected patients who were more obviously delirious; that is, more true positives. This may falsely increase sensitivity while falsely decreasing specificity. We think the differences are merely due to chance but care in data interpretation is of note. It is also of care, particularly given the age spectrum of the delirious patients, that there is not a measure of the effect of dementia and severity of illness in the diagnostic performance. Importantly, all the psychiatrists involved have a strong training in ED work. Finally, the setting of the ED here addressed is very different than most EDs particularly in the US, thus any generalizations should be of great caution. As described, here the vast majority of patients were enrolled in the EDCDU and EDIMCU and may likely comprise a minority of the more conventional ED population particularly in the US setting; more so, only 3% were evaluated in the EDPHOF which could be lower than in other places. In this context, the cohort studied may be characterized by being "sicker" and 'older'compared to other EDs, although of note that it is the delirium assessment tool currently recommended by the Geriatric Emergency Department

Guidelines is the bCAM, which is a modification of the CAM-ICU to improve the CAM-ICU's sensitivity and enhance its brevity.27,28 However, as we discussed above, there is still uncertanties of the performance of the different scales in differents EDs outside where they were validated. Ultimately, such differences may affect diagnostic performances and are here of final consideration.

Conclusion

The work indicates that the CAM-ICU European Portuguese is a practical instrument for the assessment of delirium in the real setting of an ED showing sensibility, specificity and accuracy for delirium diagnosis in the setting considered. The findings indicate for the accuracy of the CAM-ICU in delirium diagnosis, suggesting that is an appropriate tool to develop a delirium diagnostic profile in ED patients. Also, the CAM-ICU observed a prevalence of delirium of 19.8% in the ED, following previous works.23 It is expected that its systematic use in the ED will improve delirium detection rates and contribute to decrease the morbidity and mortality associated with clinical diagnosis of delirium, bridging the gap regarding to the subjectivity about delirium status. In the future, delirium should be systematically assessed in the ED and a protocol should be considered to follow-up and evaluation of delirious patients.

Declaração de Contribuição / *Contributorship Statement*:

José António Mariz – Planeamento do estudo, Análise de dados, Escrita do manuscrito

Olga Pires – Colheita de dados, Análise de dados, Revisão do manuscrito

Amândia Lopes – Colheita de dados

João Bessa, Luís Correia – Colheita de dados, revisão do manuscrito

Pedro Morgado – Colheita de dados

Jorge Teixeira, Nuno Sousa – Revisão do manuscrito

Nadine Correia Santos – Planeamento do Estudo e Escrita do Manuscrito

Responsabilidades Éticas

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CHAPTER V

General Discussion, Future Perspectives and Conclusion

1.General Discussion

It is estimated that delirium is preventable in 30-50% of all hospital cases. However, although the last 3 decades have seen major improvements in delirium research, we still fail to render hospitals prepared for its management (Salian, 2020; Fong & Inouye, 2022a). For instance, a lack of multidisciplinary dedicated (geriatric) teams, as elder individuals are the most affected age group, prevent the implementation of multicare bundles like the Hospital Elder Life Program (HELP) (Hshieh et al., 2018; Inouye et al., 2000) in medical systems, but do remind us that integrated care in delirium is proven to have impact in different levels of outcomes (Kojaie-Bidgoli et al., 2021). It is hard to face this irksome reality, but even the most assertive non-pharmacological delirium bundles fail to prevent most deliria and do little to alter the course of delirium once it begins or to improve delirium outcomes (Oldham, 2022). On the other hand, we still use antipsychotics as the mainstay of treatment, knowing that they do not fully work, or at least they have a limited, albeit not unimportant, role in the management of delirium symptoms (Andersen-Ranberg et al., 2022; Sadlonova et al., 2022). Therefore, given its complex, multifactorial etiology, treatment of delirium is likely to require pharmacological strategies that must work together with non-pharmacological ones and do so in a customized/personalized approach based on vulnerability and etiologic profiles. We know that delirium is expensive – it both comes at a cost to health systems but also to patients themselves. Knowing that it is preventable, even if it not in its entire phenomenology, the impact of any management delirium plan would be potentially enormous. To our knowledge, this could be more explicit in the ED environment, as is the starting point of care in many health systems. So far, the ADEPT approach (Shenvi et al., 2020), as discussed earlier in Chapter I, is the most structured one for use in a particular environment as is the ED, and follows a practical view of the principles (which are also behind the HELP, but more in tune with different hospital settings).

As considered throughout this thesis, delirium in the ED must, first of all, be placed in terms of Detection, Diagnosis and Assessment. Starting from the very problem of the enunciation of the topic and reaching the sophistication of the current understanding of the phenomenon, we addressed that a delirium-spectrum phenotype implies an underlying acute encephalopathy (Oldham et al., 2022). To put it simply, we have highlighted that anyone who is confronted with a patient in a busy environment in the ED must frame the treatment as discriminately as possible in neurophysiology constructs in parallel with general measures. Unfortunately, we didn't test further interventions based on a structured detection, and this is arguably the ultimate purpose to achieve, going further beyond the assessment

and closing with an (effective) intervention. However, not all deliria are the same and a nuanced approach to delirium is needed to further advance (as we did in the last years to the approach to Heart Failure (HF), Dementia or Acute Kidney Injury (AKI)). This is an aspect which has been stressed as the reason behind, for example, the failure of pharmacological treatment studies, which may be related to the heterogeneous nature of delirium (Wilson et al., 2020). Thus, establishing the degree to which delirium can be prevented, and identifying evidence-based strategies for prevention, will help inform evidence-based care pathways is essential (Martinez et al., 2015; Burton et al., 2019). A flowchart to apply in the ED is therefore proposed bellow in Figure 1. This practical flowchart follow the suggestion from Rosen et al (Rosen et al., 2015), nonetheless it's based on important international guidelines, which are evidence-based recommendations for health and care of delirium both on general grounds, and more specifically in the ED, as well as available reviews and position papers, which stress the importance of a systematic and proactive approach to delirium identification and treatment based on etiologic assessment (Leentjens et al., 2012; ;Yue et al., 2014; Carpenter et al., 2014; Mosier, Jarrod M.; Rosen, 2015; Lee et al., 2019; Davis et al., 2019; Shenvi et al., 2020; Kukolja & Kuhn, 2021; Kennedy et al., 2021; *2020 Exceptional Surveillance of Delirium: Prevention, Diagnosis and Management (NICE Guideline CG103)*, 2020). It is a practical approach, and parallel to its application we suggest also to follow the principles of the ADEPT approach outlined in Chapter I.

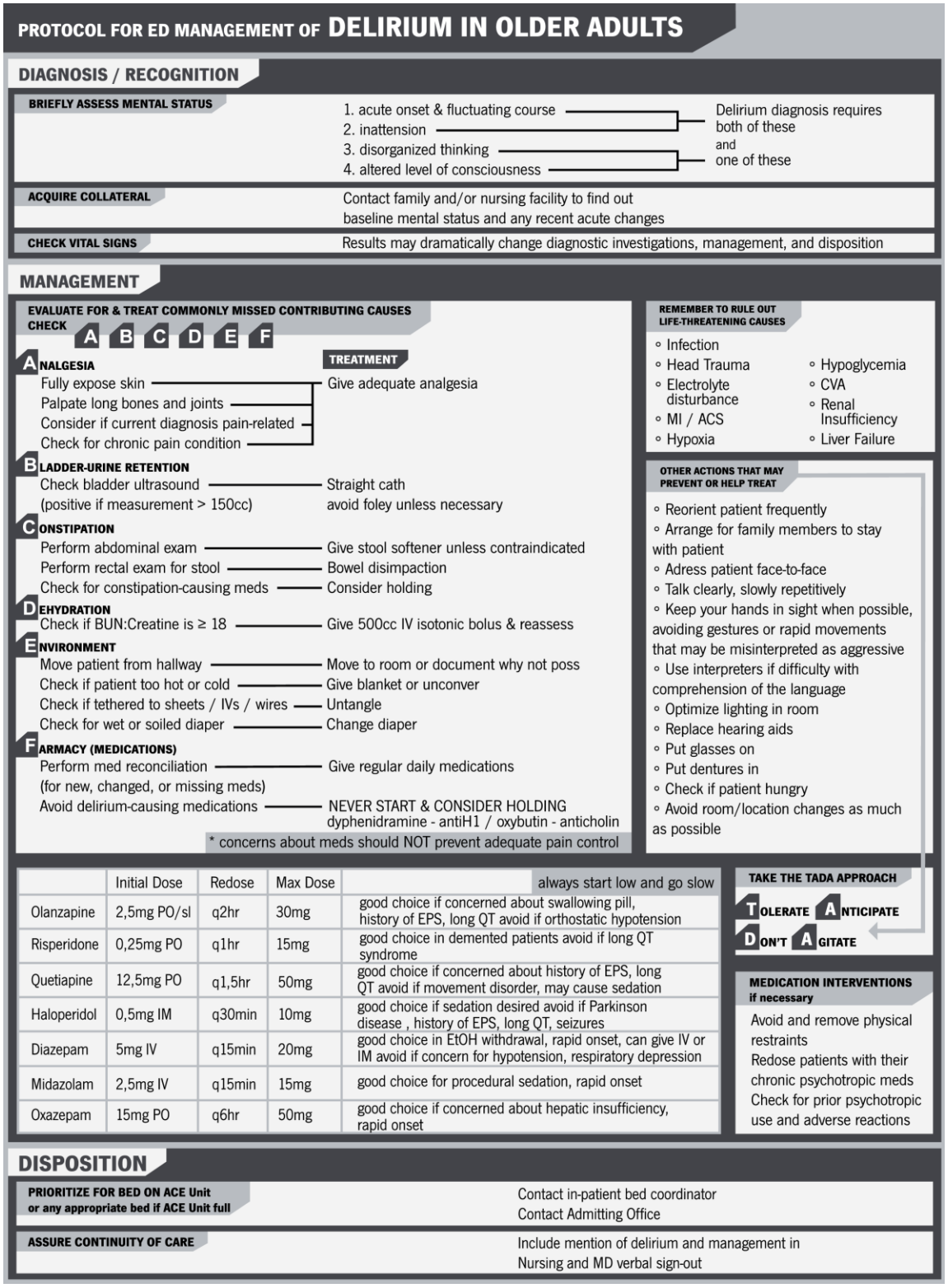


Figure 1 Novel clinical protocol for emergency department management of delirium in older adults (Adapted from: Rosen et al., 2015)

ACS, acute coronary syndrome; BUN, blood urea nitrogen; CVA, cerebrovascular accident; EPS, extrapyramidal symptom; IM, intramuscular; IV, intravenous; MI, myocardial infarction; PO, by mouth; SL, sublingual; ACE, Acute Care for the Elderly

Regarding one of the main aims of this thesis, namely, to validate the CAM-ICU Portuguese version in the ED of the Hospital of Braga, Portugal, as a delirium screening and diagnostic tool, the goal was also to achieve an acceptable sensitivity at the triage point, where nurses, for example, are the crucial practitioners to assign patients to proper venues within the ED. For this, we have evidence from the Delirium Triage Screen (DTS), which associated with the brief Confusion Assessment Method (bCAM), enable healthcare professionals, regardless of clinical background, to efficiently screen for delirium (Han et al., 2013). However, we still do not have a validation for this two-step approach in the ED beyond the United States, although our data shows good results for the CAM-ICU and the bCAM is merely a simplification of the algorithm. There are other "nurse scales" which have been tested, such as the Delirium Diagnostic Tool-Provisional (DDT-Pro) which, and in comparison to the 4 'A's test (4AT), can provisionally diagnose delirium until an expert clinician can verify it; however, these validation studies were done outside the ED (Sepúlveda et al., 2021). The 4AT is a promising tool, however, it lacks clinical implementation studies evaluating its performance, including completion rates as well as diagnostic accuracy in routine clinical practice (Tieges et al., 2021). Related to our work is the ultra-brief confusion assessment method (UB-CAM), a rapid two-step delirium identification protocol (ultra-brief screen, followed by CAM in positives), field tested with hospitalized older adults (70+) (Husser et al., 2021). Particularly, in this work, health professionals described high workload, multiple competing demands, and low morale in the practice environment during protocol implementation (Husser et al., 2021). Following this, it is not hard to predict how it would be in the ED. In Chapter II we explored the problem of the implementation, addressing the introduction of the CAM-ICU first in one of our units within the ED, including the needed period of training of the nursing team for the application of the CAM-ICU. There is a chasm between the health care we currently live in and the one which we could potentially develop based on existing knowledge (M. P. Wilson et al., 2015). In Chapter III, we further explored what was the evidence of the best tools for measurement of delirium in the ED, which was the rationale for choosing the CAM-ICU in Chapter IV (based on the extensive work done by Han et al in the ED). From here, we had to choose a practical approach to address the gold standard for Delirium in a clinical base, following as much as possible the Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines (Cohen et al., 2016) given that delirium is still diagnosed based on a strictly clinical criteria. We were confronted with the remarks by delirium experts who pointed to the lack of consultation-liaison (C - L) psychiatry representation in delirium research as a problem which has hindered the advance in delirium research. Thus, lacking a definitive gold standard for delirium diagnosis, we followed the best available "gold standard" in the field. That is, the use of the clinical

diagnosis of delirium from a systematic evaluation based on Diagnostic and Statistical Manual of Mental Disorders (DSM), by a well-trained clinical expert in the evaluation of the broad range of psychiatric and neuropsychiatric syndromes, henceforth a C-L psychiatrist well-trained in the ED milieu of the Portuguese Health System (HS) (Trzepacz & Lee, 2022). Here, we think that our HS has a great advantage having C-L psychiatrists well embedded in the ED system and permitting the needed multidisciplinary study.

Overall, we think that our work could be a solid ground to launch a national program for detection of delirium in the ED, as we still do not know the rates of delirium in our population. This will close the chasm between the health care we currently live in and the one which we could potentially develop, within the field of implementation science, known in the literature as Knowledge Translation (Lang et al., 2007; M. P. Wilson et al., 2015). Moreover, the simplification of biological markers in the ED, based on basic biochemistry and blood cell count, prioritizing Glucose, Electrolytes, Renal function, C-reactive protein and Hemogram is the rationale to identify basic modifiable risk factors ("Australian and New Zealand Society for Geriatric Medicine Position Statement Abstract: Delirium in Older People," 2016; Carpenter et al., 2019; Davis et al., 2019). Independently of the tools adopted for the identification of delirium, the common ground approach is to prevent, assessing etiologic risk groups. However, it must always be taken into consideration that any (prediction) model of prediction needs to be pragmatic, simple and to use and contemplate only routinely collected clinical data available at first assessment (Pendlebury et al., 2017). This is not so straightforward as it seems, even from sound biological standpoints, as are the neurophysiologic major mechanisms in delirium pathophysiology (J. E. Wilson et al., 2020). For example, the most difficult and fundamental work to do in the ED is the intervention with an environmental or behavioral plan, based on a nonpharmacologic way of reducing the frequency and intensity of disruptive behaviors. This simple formulation may be a cumbersome task in the ED environment. In contrast with critical care, where nurses spend a greater amount of time with each patient because of the uniquely lower patient-to-nurse ratios, providing patients with continuous reorientation (Sahawneh & Boss, 2021) is a very difficult task in the ED, independently of the mechanistic causes behind.

There is so much that we know but there is still have a long way before getting a better understanding of delirium prevention or treatment strategies and, in particular, those that provide the most compelling evidence of effectiveness and feasibility in ED settings (Dahlstrom et al., 2020). Working on the development of useful tools and protocols in the work environment of the ED (such as, alerts for drugs

with anticholinergic activity or groups of risk factors as the results of clinical history, targeted laboratory and imaging studies are obtained), cuing the prevention of medical errors concerning the premature discharges, due to under-diagnosed cases, should be one of the priorities. We can help most EDs by starting off with a mindset to change it to a friendly place. The transformation must be at national level: Characterizing the ED at different levels of reach of the population, Screening in the EDs as a starting point in the continuing of health care; and Planning the Prevention in a customized fashion. Lastly, ED researchers and clinicians must consider the role of the ED in the overall delirium prevention at the hospital level. This is increasingly important as patients endure longer ED lengths of stay as part of observation stays, and ED boarding during periods of a more complex ED workup (Kennedy et al., 2020a, 2020b).

In summary, the assimilation of the concept of a patient-centered bundled approach that (i) identifies delirium early, (ii) evaluates and addresses underlying causes, (iii) prevents complications, and (iv) promotes functional recovery is most likely to succeed. Identifying which practices belong in this bundle, and how to deliver it in a standardized, high-quality, and sustainable way, should be a major focus of the next generation of delirium treatment research (Martinez et al., 2015; Burton et al., 2019; Marcantonio, 2019).

2. Future Directions

2.1. Tools to Estimate Risk and Machine Learning

There is a need to develop simple scores to predict delirium occurrence in first-intervention settings, such as the ED, as we have previously mentioned (Zucchelli et al., 2021). The collaboration between computational scientists, or even administrative personnel, to manage databases, is fundamental for the development of risk tools more adapted to regional/local particularities. This is in line with the need of advancing our pathophysiologic understanding of delirium with a detailed and specialized understanding of risk factors and biomarkers for delirium (Fong & Inouye, 2022). Thus, with the advent of electronic patient records, delirium susceptibility could be calculated using algorithms that could be used to (i) automate individualized care and to (ii) better target multicomponent interventions locally, according to service structure, and optimize interventions that would appear unjustified according to cut-offs scores of risk (Pendlebury et al., 2017).

On this, the first steps are being taken. We have explored machine learning (ML) algorithms with Professor Ana Cristina da Silva Braga from the School of Engineering of University of Minho. Our delirium database collected at the ED (Chapter II) was used to conduct this experimental research. Available data comprised 511 records and 124 variables, including patient demographics, medications administered, admission category, urgent admission, hospitalization period, history of alcohol abuse and laboratory results (Figueiredo, 2022). It was a continuation of our first effort for identifying simple and practical risk stratification of delirium in the ED, within one of our specialized units for the treatment of urgent critical (or potentially critical) patients in the EDIMCU, as we showed in Chapter II. Particularly, this study on ML demonstrated the importance of data preparation in an ML project to obtain accurate predictions (Figueiredo, 2022). There is an enormous potential in digital medicine to improve the care of patients in a customized/personalized way, so we believe that our work could enhance the research for a precision medicine in delirium, transposing knowledge into an electronic format that could favorably disrupt the suboptimal status quo in delirium care (Tóth et al., 2020; Eeles et al., 2020). ML can even identify the high-risk population for delirium, using clinical data from electronic health records to enable automated risk estimation for each patient, and it is important to explore its risk prediction characteristics compared with the conventional risk assessment tools (Wong et al., 2018; Lee et al., 2021).

Along with this work, other steps using digital technologies have also been taken to tackle the difficulties in detecting delirium in the ED. The use of informatic applications ("apps") in the health community has surged based on the need to gather several services and functions in one informatic device (mobile phone, tablet), allowing for rapid information access and more efficient time management, among other aspects. However, many of these apps have not been evaluated or adjusted to the users' real needs. Some of our work has also tackled this issue. We have developed an app, based on the Confusion Assessment Method for Intensive Care Unit (CAM-ICU), with the software company TECField (Braga, Portugal). Its usability was evaluated with end-users (doctors and nursing staff). The diagnostic results obtained were compared with a psychiatric evaluation within our cohort of the CAM-ICU validation, and its data quality was assessed, in ED patients at the Hospital de Braga

Overall, the sample for the evaluation of the app consisted of 3 nurses from the ED with a medical-surgical specialty and two doctors, one in the specialty of Internal Medicine, working in the ED and another resident in the specialty of Anesthesia, doing internship in the context of the Operating Room and Intensive Care. Regarding the usability questionnaire (adapted Computer System Usability

Questionnaire) applied post-test to our sample, we obtained an average score of 6.59 (on a 7 point scale), which show that the app has characteristics of very good usability with end users revealing degrees of high satisfaction. Additionally, the use of the app allowed the collection of various data quickly and reported in tabular form. This feature allows the creation of an extensive database, with the advantage of not spending a lot of time - just spend the time necessary to assessment of the patient and survey of biochemical parameters and sociodemographic data included in the app. Creating this database will allow future studies in the context of delirium, addressing other issues, such as clarifying the pathophysiology, elaborate/increase the effectiveness of predictive models of delirium and associate other variables.

2.2. Cognitive impairment and Delirium

Cognitive impairment is a broad term used to describe impaired brain function that can affect a person's executive function, orientation and recall. It can be caused by several different disabilities and disorders and can be assessed using various assessment tools (Hirschman 2011). Delirium and dementia are frequent causes of cognitive impairment among older adults and have a distinct, complex, and interconnected relationship (Fong & Inouye, 2022). Various geriatric emergency department guidelines recommend routine cognitive screening of older ED patients for both chronic and acute cognitive impairment (i.e. dementia and delirium) in specialized emergency departments that have additional resources and established systems of referral (Perry et al., 2018). In fact, the long-term cognitive deficits experienced by patients after recovery from illness and delirium is an active area of research (Han et al., 2017; Lee et al., 2019). For example, there is some evidence, although not very strong, of shared biomarkers between delirium and dementia. In one study, higher IL-6, a biomarker shared between delirium and dementia, was associated with longer ED delirium duration, but only in participants without dementia (McNeil et al., 2019). On the other hand, little diagnostic research exists to guide geriatric emergency department dementia screening protocols, besides existing evidence for a trend to Abbreviated Mental Test (AMT-4) most accurately rules-in dementia, while the (Brief Alzheimer's Screen) BAS most accurately rules-out dementia (Carpenter et al., 2019).

In the continuation of the review addressing the psychometric characteristics of delirium screening tools to be applied in the ED, as we did in Chapter III, we plan to further explore what are the best tools to apply for more broad cognitive screening. Unfortunately, many cognitive assessments take more than ten minutes to complete, which is a substantial barrier to implementing them in traditional EDs (Hwang et al., 2013). However, implementing an approach which could have a start in the ED and have a

record continuing to the wards, critical units or even outpatient care, using the above-mentioned digital tools and communication technologies which are an emerging trend in healthcare and research, particularly assessing cognitive function in older adults, using The Telephone Interview for Cognitive Status-Modified – Portuguese version (TICSM-PT) (Castanho, Amorim, et al., 2016; Castanho, Portugal-Nunes, et al., 2016).

2.3. Pathophysiologic mechanisms

One of the biggest priorities for the progress in the understanding of delirium, and advocated by experts in the field, is the need to unravel distinct mechanistic routes that lead to delirium (J. E. Wilson et al., 2020). From our work, and crossing the expertise of the author of this thesis on ultrasonography in the hemodynamics evaluation, a longitudinal study – termed CONGEST-ED – has been setup in the ED of Hospital of Braga, which intends to study, with ultrasound, the hemodynamics of the congested patient. Hemodynamic congestion can precede the onset of congestive symptoms by days or weeks and is defined by growing filling pressures that occur as a compensatory response to maintain cardiac output. In this study, it is planned to add the cognitive assessment to the ultrasound data, which could open avenues for the better understanding on how hemodynamics relates to cognitive dysfunction in the real setting.

The rationale behind fluid overload influencing cognitive performance is that the interstitial edema that follows congestion, in turn, results in decreased organ perfusion, specifically in encapsulated organs like liver, kidney, and the brain (Gupta & Tomar, 2020). Furthermore, interstitial edema is hypothesized to impair tissue oxygenation by increasing the diffusion distances within the interstitium (Beaubien-Souligny et al., 2020). For example, up to 75% of patients with advanced Heart Failure (HF) have cognitive impairment and its etiopathogenesis in HF is, in particular, not well understood (Choi et al., 2022). The anatomical division by systems is fundamental, and hence the division between non-encapsulated versus encapsulated organs, the brain and kidney, which suffer the most from the effects of venous congestion. Thus, the definition of fluid tolerance arises, as well as the level that the patient can tolerate fluid administration without causing organ dysfunction. Congestive encephalopathy is taking its first steps in the jargon of clinical medicine, where, due to the “encapsulated” nature of the brain, the direct assessment of venous stress in the cerebral circulation is a challenge to clinical practice and research. On the other hand, as mentioned above, the clinical gestalt of the assessment of acute cognitive dysfunction and delirium, without the use of scales and systematic methods, has a very low sensitivity, especially in the ED. It is common to make the objective assessment of the critically ill

patient with the quick Sequential Organ Failure Assessment (qSOFA), which includes the Glasgow Coma Scale (ECG). But data are lacking that allow calibration of ECG sensitivities and specificities across the spectrum of cognitive dysfunction associated with shock states. A sensible approach is to understand the problem and apply scales aimed at assessing delirium, alongside scores such as the qSOFA. If we want to apply the concept of fluid tolerance in the sense of being "early", specific delirium assessment scales in the ED must be adopted. In the future, noninvasive methods for the study of delirium pathophysiological mechanism in patients in real setting should be developed, in parallel and oriented with research data coming from animal models which also should be pursued to drive the identification of plausible inflammatory, metabolic or neurochemical targets for interventions to minimize or prevent acute brain injury during acute illness (J. E. Wilson et al., 2020).

3. Conclusions

The present thesis focuses on: (i) the CAM-ICU European Portuguese as a practical instrument for the assessment of delirium in the real setting of an ED, showing sensibility, specificity and accuracy, for delirium diagnosis in the setting considered; (ii) age, SIRS criteria, Charlson score and creatinine, blood urea, hemoglobin and osmolarity levels, as indicators of delirium in ED patients; and (iii) the use of the CAM-ICU to assess delirium prevalence. The results show that a simple delirium prediction score could be used at the earliest point in the acute care pathway to stratify risk and to identify vulnerable groups with high care needs. This thesis also reports that the easy-of-use of the CAM-ICU scale and its feasibility and practicality are well fitted for the ED setting. Furthermore, the scale incorporates objective assessments based on the recommended DSM criteria for the diagnosis of delirium, allowing to remove any possible subjectivity from delirium assessment and rendering it easier to use by eventually less experienced users. The utilization of C-L psychiatry as a clinical "gold standard" both give strength for the use of the CAM-ICU in the ED setting by different levels of clinical practice and for the involvement of C-L psychiatry in research in delirium. Altogether these results could foment the research of delirium in the ED at a national level, from the starting point for the continuing of care across the Health System. Thus, further research is warranted to determine whether early detection alters outcome.

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