Journal of Personalized Medicine

Article

Profiling Delirium Progression in Elderly Patients via Continuous-Time Markov Multi-State Transition Models

Honoria Ocagli 1, Danila Azzolina 1, Rozita Soltanmohammadi 1, Roqaye Aliyari 1, Daniele Bottigliengo 1, Aslihan Senturk Acar 3, Lucia Stivanello 4, Mario Degan 4, Ileana Baldi 1, Giulia Lorenzoni 1 and Dario Gregori 1, 2, * 1

Citation: Ocagli, H.; Azzolina, D.; Soltanmohammadi, R.; Aliyari, R.; Bottigliengo, D.; Acar, A.S.; Stivanello, L.; Degan, M.; Baldi, I.; Lorenzoni, G.; et al. Profiling Delirium Progression in Elderly Patients via Continuous-Time Markov Multi-State Transition Models. J. Pers. Med. 2021, 11, 445. https://doi.org/10.3390/jpm11060445

Received: 25 April 2021
Accepted: 19 May 2021
Published: 21 May 2021

Publisher’s Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland.
This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

Abstract: Poor recognition of delirium among hospitalized elderlies is a typical challenge for health care professionals. Considering methodological insufficiency for assessing time-varying diseases, a continuous-time Markov multi-state transition model (CTMMTM) was used to investigate delirium evolution in elderly patients. This is a longitudinal observational study performed in September 2016 in an Italian hospital. Change of delirium states was modeled according to the 4AT score. A Cox model (CM) and a CTMMTM were used for identifying factors affecting delirium onset both with a two-state and three-state model. In this study, 78 patients were enrolled and evaluated for 5 days. Both the CM and the CTMMTM show that urine catheter (UC), aging, drugs, and invasive devices (ID) are risk factors for delirium onset. The CTMMTM model shows that transition from no-delirium/cognitive impairment to delirium was associated with aging (HR = 1.14; 95%CI, 1.05, 1.23) and neuroleptics (HR = 4.3: 1.57, 11.77), dopaminergic drugs (HR = 3.89; 1.2, 12.6), UC (HR = 2.92; 1.09, 7.79) and ID (HR = 1.67; 103, 2.71). These results are confirmed by the multivariable model. Aging, ID, antibiotics, drugs affecting the central nervous system, and absence of moving ability are identified as the significant predictors of delirium. Additionally, it seems that modeling with CTMMTM may show associations that are not directly detectable with the traditional CM.

Keywords: continuous-time Markov multi-state transition model; 4AT scale; delirium

1. Introduction

The elderly population is increasing [1] and during hospitalization, they often experienced delirium due to their age and disease severity [2,3]. However, two-thirds of cases with delirium are under-recognized [4]. Delirium has a prevalence of 1–2% in the community, 6–56% in general hospital admission [5], and 29–64% in the elderly admitted in an acute care setting [6]. Delirium onset requires longer hospitalization, extended health care services with increased risks of mortality and morbidity [2,7] in older patients.

Delirium, as an acute neuropsychiatric syndrome, is characterized by symptoms fluctuation, shift attention, impaired consciousness, and cognition disturbance like disorientation, memory impairment, and language alteration [5,8]. This mental syndrome may also include disorganized thinking, disturbance in the sleep–wake cycle, and psychomotor activity [8,9]. A complex interaction among predisposing factors (aging, baseline dementia, and functional disabilities) and precipitating ones (medications, surgery, and infection) is
responsible for this multifactorial disease [10]. Several hypotheses about delirium pathophysiology have been reported. However, the underlying mechanism is still unclear [11]. The identification and modification of precipitating factors may help in reducing delirium onset [3,12]. Recently, substantial attention has been focused on drugs and devices frequently used in the hospital setting that may induce delirium [10,12–15].

In literature, delirium outcome has been mainly addressed in prevalence [15–17] and incidence studies [18]. These approaches are useful to investigate the magnitude of the problem in a specific ward and moment. Delirium is also considered as a risk factor for clinical outcomes such as mortality in several categories of subjects; for example, COVID-19 patients [19], vascular surgery patients [20], oncological [21], and critically ill adults [22]. Delirium has also been considered a factor influencing the risk of developing other new forms of dementia [23] and as a possible issue affecting the quality of life [24]. In these research studies, the statistical methods mostly used are linear regression [16] or Cox proportional hazard model (shortly Cox model) [16,21,22]. Such methods are relevant for understanding the problem of delirium and its consequences in terms of clinical outcomes. For predictive models, instead, logistic regression [25,26] is mostly used, recently with machine learning technique [27]. The Cox model (CM) is used when considering time to define the probability of developing an event. For example, Lee et al. [28] used this model for detection of the role of frailty for delirium onset.

A Cox model analyzes the effects of several variables on survival time [29,30], considered as an event that occurs as a consequence of a previous event. However, in longitudinal studies, the same measurements are often collected in different moments and patients may experience more than two transitions.

A multi-state model (MSM), compared to a Cox model, can parameterize risk through intermediate states throughout the follow-up time. Indeed, a patient may develop intermediate states, passing from the absence of delirium to more or less severe forms of delirium. The MSM model allows to capture the risk that characterizes these transitions considering also the time elapsed from the previous event occurrence [31].

One of the most popular methods in survival analysis is the time-continuous Markov multi-state transition model in which one state depends on the previous one. Hence, MSM may help to define the transition intensities with the hazards for passing from one state to another. This model permits the consideration of covariates through the transition intensities and this helps to explain the differences of the individual in the various states and the effects of single covariate varying in the different states [31]. So, the MSM could help to discover hidden aspects behind the delirium state transition that the Cox model is unable to evaluate.

2. Materials and Methods

2.1. Aim

This work aims to identify the contributing factors for delirium onset, worsening, and transitions comparing two different statistical methods.

2.2. Design

This is a longitudinal observational study performed in September 2016 in three wards of the University Hospital of Padova: orthopedics, geriatrics, and general medicine. The current study is part of a program to create a standardized flow chart for better detection and treatment of delirium in elderly patients in the whole hospital.

2.3. Participants

Patients older than 65 years admitted to the wards involved in the study were enrolled. A hospitalization of at least five days and a good understanding of the Italian language were other additional criteria for inclusion in the study. Patients with a psychiatric illness already diagnosed during admission, with any communication problems (such as aphasia, coma status), or with a terminal disease were excluded.
2.4. Data Collection

After a maximum of 24 h since admission, a nurse evaluated the risk for delirium in patients considered eligible until the fifth day of hospitalization with the 4AT scale.

2.5. Ethical Aspects

Study design and data collection were conducted in full respect of clinical practice regulation. Data were collected in everyday clinical practice, so no further informed consent was needed. For this reason, ethical committee approval was waived.

2.6. Instrument

The 4AT scale was used for delirium detection in this study. The instrument is a simple screening tool with high sensitivity and acceptable specificity and requires no specific training [9,32]. This instrument has been used among hospitalized elderly patients, especially the ones with acute medical illnesses. The 4AT scale is based on direct observation of the patient and collection of information from various sources [33,34]. It has 0 to 12 scores: 0 suggests for no delirium, 1–3 is suggestive for cognitive impairment, and ultimately, a score equal to 4 or above suggests delirium [32,33].

2.7. Data Analysis

2.7.1. Descriptive Statistics

Descriptive statistics are summarized as follows: If the variable is the continuous median, I and III quartiles are used, and if it is categorical relative and absolute, frequencies are reported. Kruskal–Wallis type tests were performed for continuous variables and the Pearson chi-square test for categorical.

2.7.2. Sample Size

A simulation experiment was carried out for the sample size evaluation. Databases of sample size 79 were generated 400 times by a Cox model assuming an HR of 1.1 and a hospital stay time of 5 days. The data-generating model included a summarized confounding effect in two covariates (beta) including assuming the same HR of 1.1. The Cox model was calculated on all generated databases and the main effect was significant in 80.5% of the simulations.

2.7.3. Variables Collected

For each patient, socio-demographic characteristics at baseline (age, diagnosis, co-morbidities, visual and hearing impairment); physical function, physical restraint, presence/absence of invasive device, and drugs of each day were collected. For the analysis, variables were grouped as follows: (i) invasive devices, number of invasive devices (urine catheter (UC), central venous catheter (CVC), peripheral venous catheter (PVC), nasogastric feeding tubes (NG), percutaneous endoscopic gastrostomy (PEG), other device and physical restraint); (ii) basic needs, categorical variables (yes/no) which is “yes” if at least one intervention was made on the basic needs (fever or pain) during the day; (iii) number of drugs affecting the central nervous system (DACNS) (i.e., anticholinergics, dopaminergic, steroids, opioids, antiepileptics, anxiolytics, neuroleptics, and antidepressants); (iv) antibiotics, categorical variables (yes/no), which is equal to “yes” if at least one antibiotic has been administered per day (i.e., quinolones, voriconazole antifungals, and cephalosporin); (v) psychiatric pathology, categorical variables (yes/no), which is equal to “yes” if the patient is affected by dementia or depression or other psychiatric pathology; (vi) mobility aids: number of asking for aids from nursing staff per day, including the chair–bed transfer, walking, or going up/downstairs.

2.7.4. Delirium Modeling

Transition frequencies and probabilities were reported as three states (no delirium, cognitive impairment, and delirium) according to the 4AT score. A model with two states
was also created: no delirium (4AT score smaller and equal than 3) and delirium (4AT score higher than four).

Two estimation approaches were used for evaluating the hazard of the transition from one state to another: A CM and a continuous-time Markov multi-state transition model (CTM). The first approach evaluates the effect of the covariates on the transition hazards. The proportionality of hazard was evaluated using proportional hazard tests and diagnostics based on weighted residuals. The second model describes the process in which a patient moves through a series of delirium states in continuous time for longitudinal data. Data consist of observations of the process at arbitrary times so that the exact times when the delirium state changes are unobserved. The next state to which a patient moves and the time of the modification is governed by a set of transition intensities for each pair of delirium states, i and j. A transition matrix has been defined whose rows sum is zero so that the diagonal entries are defined by all transitions between delirium states are permitted (Figure 1).

![Figure 1. The Q transition intensity matrix for two states and three states modeling. The off diagonal elements in Q are rates at which subjects move into other delirium states, while the diagonal elements are transition probabilities at which subjects remain in their state. Transitions between all the states are possible.](image)

Statistical analyses were performed using R 3.3.5 [35] with rms [36], survival [37], and msm packages [38].

3. Results

In this study, 78 patients were enrolled in general medicine, geriatrics, and orthopedics hospital wards, during the 5-day study period. Table 1 reports the baseline characteristics of our sample population according to 4AT classification.

| Variables          | No Delirium | Cognitive Impairment | Delirium | Total   | p-Value |
|--------------------|-------------|----------------------|----------|---------|---------|
|                    | (n = 31)    | (n = 30)             | (n = 17) | (n = 78) |         |
| Female gender      | 52 (67%)    | 52 (67%)             | 52 (67%) | 52 (67%) | 0.597   |
| Age (year)         | 83 (76.0, 86.50) | 86.5 (82.25, 90.0) | 89 (83.0, 94.0) | 85 (80.0, 89.0) | 0.004 * |
| Age (class)        | <70         | 4 (13%)              | 0 (0%)   | 2 (12%)  | 6 (8%)  | 0.076   |
|                    | 71–75       | 3 (10%)              | 0 (0%)   | 2 (12%)  | 5 (6%)  |         |
|                    | 76–80       | 6 (19%)              | 4 (13%)  | 1 (6%)   | 11 (14%)|         |
|                    | 81–85       | 8 (26%)              | 8 (27%)  | 3 (18%)  | 19 (24%)|         |
|                    | 86–90       | 8 (26%)              | 10 (33%) | 3 (18%)  | 21 (27%)|         |
|                    | 91–95       | 1 (3%)               | 6 (20%)  | 6 (35%)  | 13 (17%)|         |
|                    | >95         | 1 (3%)               | 0 (0%)   | 2 (12%)  | 3 (4%)  |         |
Table 1. Cont.

| Variables | No Delirium | Cognitive Impairment | Delirium | Total | p-Value |
|-----------|-------------|----------------------|----------|-------|---------|
| Education | Up to school degree | 27 (87%) | 28 (93%) | 14 (82%) | 69 (88%) | 0.503 |
| Hospital wards | University degree | 4 (13%) | 2 (7%) | 3 (18%) | 9 (12%) | <0.001 * |
| | General medicine | 16 (52%) | 5 (17%) | 3 (18%) | 24 (31%) | |
| | Geriatrics | 1 (3%) | 17 (57%) | 6 (35%) | 24 (31%) | |
| | Orthopedics | 14 (45%) | 8 (27%) | 8 (47%) | 30 (38%) | |
| Drugs | Anticholinergics | 4 (13%) | 6 (20%) | 2 (12%) | 12 (15%) | 0.667 |
| | Dopaminergic | 1 (3%) | 4 (13%) | 0 (0%) | 5 (6%) | 0.13 |
| | Steroids and anti-inflammatory | 18 (58%) | 20 (67%) | 10 (59%) | 48 (62%) | 0.762 |
| | Opioids | 8 (26%) | 8 (27%) | 8 (47%) | 24 (31%) | 0.258 |
| | Antianxiety and benzodiazepine | 11 (35%) | 10 (33%) | 6 (35%) | 27 (35%) | 0.982 |
| | Neuroleptics | 1 (3%) | 5 (17%) | 8 (47%) | 14 (18%) | <0.001 * |
| | Anti-depressives | 3 (10%) | 7 (23%) | 6 (35%) | 16 (21%) | 0.097 |
| | Neuroleptic sleep | 17 (63%) | 16 (57%) | 13 (76%) | 46 (64%) | 0.421 |
| | Cephalosporin antibiotics | 2 (6%) | 7 (23%) | 0 (0%) | 9 (12%) | 0.029 * |
| | Quinolone antibiotics | 4 (13%) | 4 (13%) | 0 (0%) | 8 (10%) | 0.288 |
| | Anti-epileptic levetiracetam | 1 (3%) | 1 (3%) | 2 (12%) | 4 (5%) | 0.374 |
| Devices | Restraints | 12 (39%) | 29 (97%) | 17 (100%) | 58 (74%) | <0.001 * |
| | UC | 9 (29%) | 16 (53%) | 14 (82%) | 39 (50%) | 0.002 |
| | CVC | 0 (0%) | 2 (7%) | 2 (12%) | 4 (5%) | 0.186 |
| | PVC | 31 (100%) | 28 (93%) | 17 (100%) | 76 (97%) | 0.194 |
| | NG | 0 (0%) | 2 (7%) | 1 (6%) | 3 (4%) | 0.354 |
| | PEG | 0 (0%) | 1 (3%) | 0 (0%) | 1 (1%) | 0.445 |
| | Other devices (N) | 1 (3%) | 3 (10%) | 4 (24%) | 8 (10%) | 0.085 |
| Other devices | Colostomy | 30 (97%) | 28 (93%) | 13 (76%) | 71 (91%) | 0.139 |
| | Drainage elastomer | 0 (0%) | 1 (3%) | 3 (18%) | 4 (5%) | |
| | Physical restraint | 0 (0%) | 0 (0%) | 1 (6%) | 1 (1%) | |
| | Vac therapy | 1 (3%) | 0 (0%) | 0 (0%) | 1 (1%) | |
| | Valve | 0 (0%) | 1 (3%) | 0 (0%) | 1 (1%) | |
| Comorbidities | Dementia | 2 (6%) | 8 (27%) | 8 (47%) | 18 (23%) | 0.005 * |
| | Alcoholism | 1 (3%) | 0 (0%) | 0 (0%) | 1 (1%) | 0.464 |
| | Drugs addiction | 1 (3%) | 0 (0%) | 0 (0%) | 1 (1%) | 0.464 |
| | Depression | 2 (6%) | 4 (13%) | 0 (0%) | 6 (8%) | 0.243 |
| | Previous delirium | 0 (0%) | 2 (7%) | 1 (6%) | 3 (4%) | 0.354 |
| | Other psychiatry pathologies | 1 (3%) | 0 (0%) | 2 (12%) | 3 (4%) | 0.128 |
| | Diabetes | 7 (23%) | 4 (13%) | 5 (29%) | 16 (21%) | 0.395 |
| | Cancers | 10 (32%) | 11 (37%) | 8 (47%) | 29 (37%) | 0.596 |
| | Malnutrition-Dehydration | 10 (32%) | 13 (43%) | 7 (41%) | 30 (38%) | 0.651 |
| | Surgery history | 0 (0%) | 1 (3%) | 3 (18%) | 4 (5%) | 0.025 |
| | Previous admission | 27 (87%) | 29 (97%) | 16 (94%) | 72 (92%) | 0.356 |
| | Visual disabilities | 13 (42%) | 7 (23%) | 9 (53%) | 29 (37%) | 0.102 |
| | Hearing disabilities | 8 (26%) | 11 (37%) | 10 (59%) | 29 (37%) | 0.077 |
| Bed to chair transferring ability | 0 | 13 (42%) | 20 (67%) | 16 (94%) | 49 (63%) | <0.001 * |
| | 5 | 7 (23%) | 9 (30%) | 1 (6%) | 17 (22%) | |
| | 10 | 11 (35%) | 1 (3%) | 0 (0%) | 12 (15%) | |
| Walking ability | 0 | 13 (42%) | 24 (80%) | 17 (100%) | 54 (69%) | <0.001 * |
| | 5 | 9 (29%) | 5 (17%) | 0 (0%) | 14 (18%) | |
| | 10 | 9 (29%) | 1 (3%) | 0 (0%) | 10 (13%) | |
Table 1. Cont.

| Variables                      | No Delirium | Cognitive Impairment | Delirium | Total | p-Value |
|--------------------------------|-------------|----------------------|----------|-------|---------|
|                                | (n = 31)    | (n = 30)             | (n = 17) | (n = 78) |         |
| Stairs going down ability      |             |                      |          |        |         |
| 0                              | 21 (68%)    | 28 (93%)             | 17 (100%)| 66 (85%)| 0.02 *  |
| 5                              | 5 (16%)     | 1 (3%)               | 0 (0%)   | 6 (8%)  |         |
| 10                             | 5 (16%)     | 1 (3%)               | 0 (0%)   | 6 (8%)  |         |
| Pain                           |             |                      |          |        |         |
| 19                             | 19 (61%)    | 14 (47%)             | 7 (41%)  | 40 (51%)| 0.334   |
| 5                              | 5 (16%)     | 1 (3%)               | 0 (0%)   | 6 (8%)  |         |
| Fever                          |             |                      |          |        |         |
| 6                              | 6 (19%)     | 5 (17%)              | 5 (29%)  | 16 (21%)| 0.57    |
| ICD diagnosis                  |             |                      |          |        |         |
| Circulatory and connective tissue | |                   |          |        |         |
| 14                             | 16 (52%)    | 20 (67%)             | 8 (47%)  | 44 (56%)| 0.2     |
| Digestive                      |             |                      |          |        |         |
| 0                              | 14 (45%)    | 8 (27%)              | 8 (47%)  | 30 (38%)|         |
| Respiratory                    |             |                      |          |        |         |
| 1                              | 1 (3%)      | 0 (0%)               | 0 (0%)   | 1 (1%)  |         |
| Symptoms, signs, and undefined morbidity states | |                   |          |        |         |
| 0                              | 0 (0%)      | 2 (7%)               | 0 (0%)   | 2 (3%)  |         |

*p-value < 0.001; Abbreviation; CI: cognitive impairment, UC: urine catheter, CVC: central venous catheter, PVC: peripheral venous catheter, NG: nasogastric tube, PEG: percutaneous endoscopic gastrostomy, DACNS: drugs affecting central nervous system.

At admission time, 17 patients experienced delirium, 31 patients reported no delirium, and 30 cognitive impairment. Patients that experienced delirium were older (89) compared with the other two groups (median age of 83 and 86.5), prevalently female (52, 67%) with a lower middle school. Drugs mostly used were steroids and anti-inflammatory (48, 62%) along with drugs for inducing sleeping (46, 64%). Peripheric venous catheters were the device mostly used in these patients (76, 97%) along with physical restraints (58, 74%). Dementia history was the comorbidities mostly present in all the groups. Hearing and visual impairments, respectively (10, 59%) and (9, 53%), were mainly present in patients at risk for delirium.

3.1. Transition Frequencies and Probabilities

The transition frequencies and probabilities for three-state and two-state delirium are reported in Table 2.

Table 2. The observed number of transitions and transitions probabilities (%) for three and two delirium states.

| Three Delirium States | No Delirium | Cognitive Impairment | Delirium |
|-----------------------|-------------|----------------------|----------|
|                       | (n = 124)   | (n = 6)              | (n = 1)  |
| No delirium           | (95; 0.40–0.97) | (5; 2–11)           | (1; 0.3–0.52) |
| Cognitive impairment  | 8           | 80                   | 18       |
| (8; 3–14)             |             | (75; 65–83)         | (17; 11–26) |
| Delirium              | 2           | 13                   | 60       |
| (3; 1–13)             |             | (17; 11–28)         | (80; 66–87) |

| Two Delirium States   | No delirium—Cognitive Impairment | Delirium |
|-----------------------|----------------------------------|----------|
|                       | (n = 218)                        | (n = 19) |
| No delirium           | (92; 88–95)                      | (8; 5–12) |
| Cognitive impairment  | 15                               | 60       |
| (20; 13–31)           |                                  | (80; 70–87) |
| Delirium              | 60                               |         |
| (3; 1–13)             |                                  |         |

The highest number of transitions in the three-state case were observed from cognitive impairment to delirium with 18 episodes and its opposite direction with 13 individuals with a transition probability of 17% in both directions. In two-state cases instead, 19 episodes were observed to pass from no-delirium/cognitive impairment to delirium and 15 in the opposite direction. In this case, the probability of passing in the first direction is very low 8% (95% CI: 0.05, 0.12) and in the opposite of 20% (95% CI: 0.13, 0.31).
3.2. Cox model and Continuous-Time Markovian Multi-State Transition Model

The results of the two state-delirium models both for the Cox model and the continuous-time Markovian multi-state transition model were compared and reported in Table 3.

Table 3. Proportional transition Cox hazards and continuous-time Markovian multi-state transition two-states model (95% CI).

The proportionality of hazard has been evaluated using proportional hazards tests and diagnostics based on weighted residuals.

| Proportional Transition Cox Hazard Model | Continuous-Time Markovian Multi-State Transition Model |
|-----------------------------------------|-------------------------------------------------------|
| ND-CI to D | D to ND-CI | ND-CI to D | D to ND-CI |
| HR | HR | HR | HR |
| (95%CI) | (95%CI) | (95%CI) | (95%CI) |
| 20.38 | 2.2 | 2.92 | 1.8 |
| (2.72, 152.9) | (0.49, 9.81) | (1.09, 7.79) | (0.4, 8.05) |
| 0.76 | 1.09 | 0.86 | 0.91 |
| (0.61, 0.94) | (0.81, 1.48) | (0.73, 1) | (0.6, 1.38) |
| 0.82 | 1.36 | 0.86 | 1.05 |
| (0.68, 0.99) | (0.88, 2.11) | (0.72, 1.03) | (0.7, 1.57) |
| 0.88 | 1.61 | 0.9 | 1.28 |
| (0.72, 1.07) | (1.01, 2.55) | (0.64, 1.25) | (0.87, 1.89) |
| 1.24 | 0.93 | 1.61 | 1.18 |
| (0.41, 3.79) | (0.32, 2.73) | (0.52, 4.96) | (0.4, 3.52) |
| 1.25 | 0.7 | 1.48 | 0.96 |
| (0.5, 3.09) | (0.25, 2.01) | (0.58, 3.73) | (0.34, 2.68) |
| 1.16 | 0.19 | 1.35 | 0.88 |
| (0.33, 4.02) | (0.33, 1.48) | (0.38, 4.71) | (0.27, 2.8) |
| 1.93 | 1.25 | 2.2 | 1.25 |
| (0.78, 4.77) | (0.45, 3.45) | (0.88, 5.53) | (0.45, 3.52) |
| 2.21 | 1.15 | 4.3 | 1.28 |
| (0.73, 6.72) | (0.4, 3.29) | (1.57, 11.77) | (0.44, 3.57) |
| 1.05 | 0.83 | 0.46 | 0.75 |
| (0.42, 2.68) | (0.28, 2.43) | (0.15, 1.39) | (0.25, 2.21) |
| 1.97 | 0.89 | 2.6 | 1.14 |
| (0.71, 5.49) | (0.28, 2.81) | (0.96, 7.09) | (0.38, 3.42) |
| 1.72 | 0.92 | 1.33 | 1.02 |
| (0.69, 4.78) | (0.21, 4.12) | (0.43, 4.13) | (0.22, 4.6) |
| 2.63 | 0.89 | 3.89 | 1.13 |
| (0.78, 9.07) | (0.11, 6.9) | (1.2, 12.6) | (0.14, 9.28) |
| 0.5 | 0.31 | 0.46 | 0.3 |
| (0.07, 3.78) | (0.04, 2.38) | (0.06, 3.47) | (0.04, 2.32) |
| 2.34 | 0.89 | 2.37 | 0.93 |
| (0.89, 6.16) | (0.32, 2.51) | (0.88, 6.38) | (0.33, 2.68) |
| 0.97 | 0.63 | 0.91 | 0.61 |
| (0.37, 2.54) | (0.2, 2) | (0.34, 2.42) | (0.19, 1.94) |
| 1.13 | 0.99 | 1.14 | 1 |
| (1.05, 1.22) | (0.92, 1.06) | (1.05, 1.23) | (0.93, 1.07) |
| 0.79 | 1.09 | 0.8 | 1.07 |
| (0.23, 2.7) | (0.35, 3.42) | (0.23, 2.79) | (0.34, 3.41) |
| 1.71 | 1.02 | 1.74 | 1.03 |
| (0.67, 4.34) | (0.37, 2.81) | (0.67, 4.49) | (0.37, 2.89) |
| 2.06 | 0.81 | 1.67 | 0.79 |
| (1.28, 3.3) | (0.4, 1.66) | (1.03, 2.71) | (0.37, 1.7) |
| 1.21 | 0.47 | 1.45 | 0.95 |
| (0.48, 3.03) | (0.17, 1.33) | (0.56, 3.75) | (0.32, 2.82) |
| 1.44 | 1 | 1.36 | 1.01 |
| (1.03, 2) | (0.64, 1.56) | (0.94, 1.95) | (0.65, 1.58) |
| 2.24 | 1.24 | 2.46 | 1.19 |
| (0.9, 5.58) | (0.45, 3.42) | (0.97, 6.25) | (0.42, 3.35) |
| 2.63 | 1.13 | 1.67 | 0.91 |
| (1.05, 6.54) | (0.52, 1.4) | (0.62, 4.5) | (0.2, 4.12) |
| 0.85 | 0.95 | 0.94 | 1.03 |
| (0.14, 0.99) | (0.14, 1.31) | (0.87, 1.02) | (0.86, 1.23) |

Abbreviation: ND: no delirium, CI: cognitive impairment, D: delirium, HR: hazard ratio.
In both models, the urine catheter increased the transition from no-delirium/cognitive impairment to delirium (HR = 20.38; 95% CI: 2.72, 152.9) in the Cox model and 2.92 (95% CI: 1.09, 7.79) in the MSM model. Additionally, age and a higher number of invasive devices increase the transition from no-delirium/cognitive impairment to delirium in both models, similar with strength. Drugs such as neuroleptic (HR = 4.3; 95% CI, 1.57, 11.77) and dopaminergic (HR = 3.89; 95% CI, 1.2, 12.6) increased the hazard from no-delirium/cognitive impairment to delirium in the MSM, in the Cox model, drugs influence the increase of the hazard when grouped in DACNS.

3.3. Multivariable Analysis

Multivariable analysis of the Cox model (Table 4) showed that older individuals (HR = 1.11; 95% CI, 1.03, 1.2) and subjects with more use of invasive devices (HR = 1.83; 95% CI, 1.13, 2.97) had a higher hazard risk of moving from no-delirium/cognitive impairment to delirium state.

Table 4. Multivariable proportional transition Cox hazards model and continuous-time Markovian multi-state transition model (two-states, 95% CI).

| Variables                  | No Delirium-Cognitive Impairment to Delirium | Delirium to No Delirium-Cognitive Impairment |
|----------------------------|---------------------------------------------|---------------------------------------------|
|                            | HR (95% CI)                                 | HR (95% CI)                                 |
| Age                       | 1.11 (1.03, 1.2)                            | 0.98 (0.91, 1.06)                           |
| Invasive devices (number) | 1.83 (1.13, 2.97)                           | 0.78 (0.37, 1.62)                           |

Continuous-Time Markovian Multi-state

| Variables                  | HR (95% CI)                                 |
|----------------------------|---------------------------------------------|
| Age                       | 1.12 (1.03, 1.21)                           |
| Invasive devices (number) | 1.43 (0.85, 2.38)                           |
|                            | 0.99 (0.92, 1.07)                           |
|                            | 0.78 (0.36, 1.69)                           |

Abbreviation; CI: cognitive impairment.

According to our multivariable Markovian findings, delirium risk among subjects with no-delirium/cognitive impairment increased with increasing of age (HR = 1.12; 95% CI, 1.03, 1.21).

4. Discussion

Although delirium frequently occurs among the hospitalized elderly population, its understanding is still insufficient among caregiver providers.

Our results are in agreement with the literature findings concerning the associations between delirium and the use of invasive devices, [14,15] utilization of drugs affecting the central nervous system such as neuroleptic and anti-depressive [3,15,30,39,40], administration of antibiotics [10], and age [2,10,11,41,42]. For what concerns drugs, delirium seems to be caused by brain activities in dopaminergic overflow and/or anticholinergic deficiency [10] and psychoactive drugs work in the same neurotransmitter pathways. Another relevant factor influencing delirium onset is aging, which produces physiological changes such as cholinergic system atrophy [43]. Moreover, elderly people face multi-morbidity conditions and consequently, the need for multiple drug therapy will increase [44]. Hence, synergetic drug reactions, their relevant adverse events may cause aging-induced pharmacokinetic alteration to effect treatment or even exacerbate the condition [44]. These results are confirmed by both models and the multivariable analysis, with some differences for what concerns the strength of the HR.

The level of mobilization is also a factor that influences the delirium onset, our results show that patients who had a higher level of functional activity (i.e., walking), had a lower probability of facing delirium as already found by in Solà-Miravete [45].

Our results also show that there are numerous transitions between cognitive impairment and delirium states. This phenomenon is remarkable, considering the short follow-up period. This could mean that in longer period, patients may experience different delirium
status depending on different moments, for example, after a procedure or administration of a new medication. This multiplicity of delirium status in a single patient should be taken into consideration when working on predictive models for delirium detection or for studies that consider risk factors for delirium. Cognitive impairment in elderly increases the probability of several acute medical problems and might lead to poor prognosis, and as reported by a systematic review, it is a strong risk factor for delirium onset [11]. It has been reported that 20% of delirium prevalence was among older patients with cognitive impairment [46]. So, early detection following with pharmacological and non-pharmacological approaches can prevent it [47].

The studies on delirium are usually based on a single-point assessment, and they usually do not include the changes that patients underwent during their hospital stay. A recent study has developed a “dynamic” predictive tool for delirium in ICU patients [26]. In this study, the authors consider all the risk factors for delirium that “could come and go prior to the onset of delirium”. However, even in this case, delirium evaluation was based on a single assessment. Hence, the use of models that consider time in their structure could be helpful to better understand delirium progression, as our work suggests.

Both methods are suitable in the condition of delirium evolution, both show similar results in identifying risk factors for delirium onset. However, some differences have to be taken into account when comparing these two methods. In the Cox model, which is appropriate for survival analysis with censored data and time-varying covariates, the outcomes depend only on prognostic factors [48]. It also considers the concepts of interaction and collinearity of independent variables [49]. MSM provides a broader biological understanding about obscure aspects of disease endpoints, which are commonly away from caregivers’ attention during the study [50]. As in our case, the Markovian multi-state model is helpful in situations where a patient can experience different states and can make transitions between the states. This model is a more realistic tool for comparison with the discrete-time model since it would allow transitions among states to happen at any time of the follow-up. Moreover, since it is a continuous-time model, it is preferable as it takes into account the transitions that may have a small probability [51]. Thus, in delirium progression, the continuous-time Markov multi-state transition model as a flexible approach supported the Cox model, which is more naïve but essential in addressing the needs of health care professionals. Ultimately, the utilization of 4AT with good sensitivity and acceptable specificity has simplified delirium detection due to no complicated training needs [40].

Limitations

These results should be interpreted carefully, due to a couple of limitations. To begin with, the small sample size of this study should be taken into consideration with caution, as it does not allow to use more collected risk factors in our models. The small follow-up period of observation might also be an obstacle for the identification of delirium which can be experienced with high frequency in a longer follow-up.

5. Conclusions

According to our results, older age, drugs, particularly those affecting the central nervous system, and invasive devices play an important role in delirium onset. Except for age, drugs and invasive devices are modifiable risk factors, and they should be carefully prescribed and used in this frail population. Moreover, by obtaining the pharmaceutical history of patients in the admission time and identification of any drugs as the potential reasons for delirium or whether it can worsen its condition, the administration should be stopped and an alternative pharmaceutical one should be prescribed.

In conclusion, in this study, we adopted two different statistical approaches to model the change in delirium status of a group of elderly patients admitted to hospital experiencing different stages of the 4AT scale. The choice of considering several states and related transitions can provide a set of more detailed information if compared with an approach
that considers a single endpoint, such as the Cox model, where it is not possible to include an intermediate state such as the cognitive impairment, which is a frequently observed state and also a risk factor for delirium onset. In this sense, MSM shows associations that are not directly detectable with the Cox model. MSM model may be helpful with a larger cohort of patients for the prediction of incidence and prevalence over the larger time horizon.

**Author Contributions:** Conceptualization, D.G. and I.B.; methodology, I.B. and D.A.; formal analysis, D.A. and R.A.; data curation, R.S.; writing—original draft preparation, H.O. and R.S.; writing—review and editing, D.B., A.S.A., G.L.; supervision, D.G. and G.L.; project administration, L.S. and M.D. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** The study was conducted according to the guidelines of the Declaration of Helsinki. Ethical review and approval were waived for this study, since data were collected in everyday clinical practice.

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy.

**Conflicts of Interest:** The authors declare no conflict of interest.

**References**

1. Strijbos, M.J.; Steunenberg, B.; Van der Mast, R.C.; Inouye, S.K.; Schuurmans, M.J. Design and Methods of the Hospital Elder Life Program (HELP), a Multicomponent Targeted Intervention to Prevent Delirium in Hospitalized Older Patients: Efficacy and Cost-Effectiveness in Dutch Health Care. *BMC Geriatr.* 2013, 13, 78. [CrossRef]

2. Fortini, A.; Monettini, A.; Tavernese, G.; Facchini, S.; Tofani, L.; Pazzi, M. Delirium in Elderly Patients Hospitalized in Internal Medicine Wards. *Intern. Emerg. Med.* 2014, 9, 435–441. [CrossRef] [PubMed]

3. Burry, L.D.; Williamson, D.R.; Mehta, S.; Perreault, M.M.; Mantas, I.; Mallick, R.; Fergusson, D.A.; Smith, O.; Fan, E.; Dupuis, S. Delirium and Exposure to Psychoactive Medications in Critically Ill Adults: A Multi-Centre Observational Study. *J. Crit. Care 2017, 42, 268–274.* [CrossRef]

4. Hendry, K.; Quinn, T.J.; Evans, J.; Scortichini, V.; Miller, H.; Burns, J.; Cunnington, A.; Stott, D.J. Evaluation of Delirium Screening Tools in Geriatric Medical Inpatients: A Diagnostic Test Accuracy Study. *Age Ageing 2016, 45, 832–837.* [CrossRef] [PubMed]

5. Poepoe, D.M. Delirium in Older Adults. *Mt. Sinai J. Med.* 2011, 78, 571–582. [CrossRef] [PubMed]

6. Mossello, E.; Tesi, F.; Santo, S.G.D.; Mazzone, A.; Torrini, M.; Cherubini, A.; Bo, M.; Musicco, M.; Bianchetti, A.; Ferrari, A.; et al. Recognition of Delirium Features in Clinical Practice: Data from the “Delirium Day 2015 National Survey. *J. Am. Geriatr. Soc. 2018, 66, 302–308.* [CrossRef] [PubMed]

7. Fong, T.G.; Tulebaev, S.R.; Inouye, S.K. Delirium in Elderly Adults: Diagnosis, Prevention and Treatment. *Nat. Rev. Neurol. 2009, 5, 210.* [CrossRef]

8. Maldonado, J.R. Delirium in the Acute Care Setting: Characteristics, Diagnosis and Treatment. *Crit. Care Clin. 2008, 24, 657–722.* [CrossRef]

9. Morandi, A.; Di Santo, S.G.; Cherubini, A.; Mossello, E.; Meagher, D.; Mazzone, A.; Bianchetti, A.; Ferrara, N.; Ferrari, A.; Musicco, M.; et al. Clinical Features Associated with Delirium Motor Subtypes in Older Inpatients: Results of a Multicenter Study. *Am. J. Geriatr. Psychiatry 2017, 25, 1064–1071.* [CrossRef]

10. Alagiakrishnan, K.; Wiens, C.A. An Approach to Drug Induced Delirium in the Elderly. *Postgrad. Med. J. 2004, 80, 388–393.* [CrossRef]

11. Tomlinson, E.J.; Phillips, N.M.; Mohebbi, M.; Hutchinson, A.M. Risk Factors for Incident Delirium in an Acute General Medical Setting: A Retrospective Case–Control Study. *J. Clin. Nurs. 2017, 26, 658–667.* [CrossRef]

12. Kim, S.-Y.; Kim, S.-W.; Kim, J.-M.; Shim, I.-S.; Bae, K.-Y.; Shim, H.-J.; Bae, W.-K.; Cho, S.-H.; Chung, I.-J.; Yoon, J.-S. Differential Associations Between Delirium and Mortality According to Delirium Subtype and Age: A Prospective Cohort Study. *Psychosom. Med. 2015, 77, 903–910.* [CrossRef] [PubMed]

13. Swart, L.M.; van der Zanden, V.; Spies, P.E.; de Roorij, S.E.; van Munster, B.C. The Comparative Risk of Delirium with Different Opioids: A Systematic Review. *Drugs Aging 2017, 34, 437–443.* [CrossRef] [PubMed]

14. Bo, M.; Porrino, P.; Di Santo, S.G.; Mazzone, A.; Cherubini, A.; Mossello, E.; Bianchetti, A.; Musicco, M.; Ferrari, A.; Ferrara, N. The Association of Indwelling Urinary Catheter with Delirium in Hospitalized Patients and Nursing Home Residents: An Explorative Analysis from the “Delirium Day 2015”. *Aging Clin. Exp. Res. 2019, 31, 411–420.* [CrossRef] [PubMed]
15. Bellelli, G.; Morandi, A.; Di Santo, S.G.; Mazzone, A.; Cherubini, A.; Mossello, E.; Bo, M.; Bianchetti, A.; Rozzini, R.; Zanetti, E.; et al. “Delirium Day”: A Nationwide Point Prevalence Study of Delirium in Older Hospitalized Patients Using an Easy Standardized Diagnostic Tool. BMC Med. 2016, 14. [CrossRef] [PubMed]

16. Rebora, P.; Rozzini, R.; Bianchetti, A.; Blangiardo, P.; Marchegiani, A.; Piazzoli, A.; Mazzeo, F.; Cesaroni, G.; Chizzioli, A.; Guerini, F.; et al. Delirium in Patients with SARS-CoV-2 Infection: A Multicenter Study. J. Am. Geriatr. Soc. 2021, 69, 293–299. [CrossRef] [PubMed]

17. Therneau, T.; Lumley, T. Multi-State Modelling with R: The Msm Package. [msm-manual.pdf (accessed on 25 April 2021)].

18. Mauri, V.; Reuter, K.; Körber, M.I.; Wiemann, H.; Lee, S.; Egghalzadeh, K.; Kuhn, E.; Baldus, S.; Kelm, M.; Nickenig, G.; et al. Incidence, Risk Factors and Impact on Long-Term Outcome of Postoperative Delirium After Transcatheter Aortic Valve Replacement. Front. Cardiovasc. Med. 2021, 8, 645724. [CrossRef]

19. Pranata, R.; Huang, I.; Lim, M.A.; Yonas, E.; Vania, R.; Kuswardhani, R.A.T. Delirium and Mortality in Coronavirus Disease 2019 (COVID-19)-A Systematic Review and Meta-Analysis. Arch. Gerontol. Geriatr. 2021, 95, 104388. [CrossRef]

20. Visser, L.; Prent, A.; Huber, L.; van Leeuwen, B.; Zeebregts, C.J.; Pol, R.A. Risk Factors for Delirium after Vascular Surgery: A Systematic Review and Meta-Analysis. Ann. Visc. Surg. 2021. [CrossRef]

21. Seiler, A.; Blum, D.; Deuel, J.W.; Hertler, C.; Schottle, M.; Zipser, C.M.; Ernst, J.; Schubert, M.; von Känel, R.; Boettiger, S. Delirium Is Associated with an Increased Morbidity and In-Hospital Mortality in Cancer Patients: Results from a Prospective Cohort Study. Palliat. Support. Care. 2021, 1–10. [CrossRef]

22. Duprey, M.S.; van den Boogaard, M.; van der Hoeven, J.G.; Pickkers, P.; Briesacher, B.A.; Saczynski, J.S.; Griffith, J.L.; Devlin, J.W. Association between Incident Delirium and 28- and 90-Day Mortality in Critically Ill Adults: A Secondary Analysis. Crit. Care 2020, 24, 161. [CrossRef] [PubMed]

23. Pereira, J.V.-B.; Aung Thein, M.Z.; Nitchingham, A.; Caplan, G.A. Delirium in Older Adults Is Associated with Development of New Dementia: A Systematic Review and Meta-Analysis. Int. J. Geriatr. Psychiatry 2021. [CrossRef] [PubMed]

24. DeBolt, C.L.; Gao, Y.; Sutter, N.; Soong, A.; Leard, L.; Jeffrey, G.; Kleinhenz, M.E.; Calabrese, D.; Greenland, J.; Venado, A.; et al. The Association of Post-Operative Delirium with Patient-Reported Outcomes and Mortality after Lung Transplantation. Clin. Transpl. 2021, e14275. [CrossRef]

25. Chen, X.; Lao, Y.; Zhang, Y.; Qiao, L.; Zhuang, Y. Risk Predictive Models for Delirium in the Intensive Care Unit: A Systematic Review and Meta-Analysis. Ann. Palliat. Med. 2021, 10, 1467–1479. [CrossRef]

26. Fan, H.; Ji, M.; Huang, J.; Yue, Y.; Yang, X.; Wang, C.; Ying, W. Development and Validation of a Dynamic Delirium Prediction Rule in Patients Admitted to the Intensive Care Units (DYNAMIC-ICU): A Prospective Cohort Study. Int. J. Nurs. Stud. 2019, 93, 64–73. [CrossRef] [PubMed]

27. Jauk, S.; Kramer, D.; Großauer, B.; Riemmüler, S.; Avian, A.; Berghold, A.; Leodolter, W.; Schulz, S. Risk Prediction of Delirium in Hospitalized Patients Using Machine Learning: An Implementation and Prospective Evaluation Study. J. Am. Med. Inf. Assoc. 2020, 27, 1383–1392. [CrossRef]

28. Lee, S.-Y.; Wang, J.; Chao, C.-T.; Chien, K.-L.; Huang, J.-W. Frailty Is Associated with a Higher Risk of Developing Delirium and Cognitive Impairment among Patients with Diabetic Kidney Disease: A Longitudinal Population-Based Cohort Study. Diabet. Med. 2021, e14566. [CrossRef]

29. Fisher, L.D.; Lin, D.Y. Time-Dependent Covariates in the Cox Proportional-Hazards Regression Model. Annu. Rev. Public Health 1999, 20, 145–157. [CrossRef] [PubMed]

30. Weaver, C.B.; Kane-Gill, S.L.; Gunn, S.R.; Kirisci, L.; Smithburger, P.L. A Retrospective Analysis of the Effectiveness of Antipsychotics in the Treatment of ICU Delirium. J. Crit. Care 2017, 41, 234–239. [CrossRef]

31. Meira-Machado, L.; de Uña-Álvarez, C.; Andersen, P.K. Multi-State Models for the Analysis of Time-to-Event Data. Stat. Methods Med. Res. 2009, 18, 195–222. [CrossRef] [PubMed]

32. Marcantonio, E.R. Delirium in Hospitalized Older Adults. N. Engl. J. Med. 2017, 377, 1456–1466. [CrossRef]

33. Kuladee, S.; Prachason, T. Development and Validation of the Thai Version of the 4 ‘A’s Test for Delirium Screening in Hospitalized Elderly Patients. Psychogeriatrics 2019, 19, 445–453. [CrossRef]

34. Bellelli, G.; Morandi, A.; Davis, D.H.J.; Mazzola, P.; Turco, R.; Gentile, S.; Ryan, T.; Cash, H.; Guerini, F.; Torpilliesi, T.; et al. Validation of the 4AT, a New Instrument for Rapid Delirium Screening: A Study in 234 Hospitalised Older People. Int. J. Geriatr. Psychiatry 2017, 32, 234–239. [CrossRef] [PubMed]

35. R Core Team. R: A Language and Environment for Statistical Computing; R Foundation for Statistical Computing: Vienna, Austria, 2020.

36. Harrell, F.E., Jr. Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis; Springer: Berlin/Heidelberg, Germany, 2015; ISBN 3-540-19425-9.

37. Therneau, T.; Lumley, T. R Survival Package. 2013. Available online: https://cran.r-project.org/web/packages/msm/vignettes/msm-manual.pdf (accessed on 25 April 2021).

38. Jackson, C. Multi-State Modelling with R: The Msm Package; MRC Biostatistics Unit: Cambridge UK, 2019.

39. Ebersbach, G.; Ip, C.W.; Klebe, S.; Koschel, J.; Lorenzl, S.; Schrader, C.; Winkler, C.; Franke, C. Management of Delirium in Parkinson’s Disease. J. Neural. Transm. 2019, 126, 905–912. [CrossRef]
40. Pasina, L.; Colzani, L.; Cortesi, L.; Tettamanti, M.; Zambon, A.; Nobili, A.; Mazzone, A.; Mazzola, P.; Annoni, G.; Bellelli, G. Relation Between Delirium and Anticholinergic Drug Burden in a Cohort of Hospitalized Older Patients: An Observational Study. *Drugs Aging* 2019, 36, 85–91. [CrossRef] [PubMed]

41. Schreiber, M.P.; Colantuoni, E.; Bienvenu, O.J.; Neufeld, K.J.; Chen, K.-F.; Shanholtz, C.; Mendez-Tellez, P.A.; Needham, D.M. Corticosteroids and Transition to Delirium in Patients with Acute Lung Injury. *Crit. Care Med.* 2014, 42, 1480–1486. [CrossRef] [PubMed]

42. Ryan, D.J.; O’Regan, N.A.; Caoimh, R.O.; Clare, J.; O’Connor, M.; Leonard, M.; McFarland, J.; Tighe, S.; O’Sullivan, K.; Trzepacz, P.T.; et al. Delirium in an Adult Acute Hospital Population: Predictors, Prevalence and Detection. *BMJ Open* 2013, 3. [CrossRef] [PubMed]

43. Wolters, A.E.; Zaal, I.J.; Veldhuijzen, D.S.; Cremer, O.L.; Devlin, J.W.; van Dijk, D.; Slooter, A.J.C. Anticholinergic Medication Use and Transition to Delirium in Critically Ill Patients: A Prospective Cohort Study. *Crit. Care Med.* 2015, 43, 1846–1852. [CrossRef] [PubMed]

44. Hein, C.; Forgues, A.; Plau, A.; Sommet, A.; Vellas, B.; Nourhashemi, F. Impact of Polypharmacy on Occurrence of Delirium in Elderly Emergency Patients. *J. Am. Med Dir. Assoc.* 2014, 15, 850.e11–850.e15. [CrossRef] [PubMed]

45. Solà-Miravete, E.; López, C.; Martinez-Segura, E.; Adell-Lleixà, M.; Juvé-Udina, M.E.; Lleixà-Fortuño, M. Nursing Assessment as an Effective Tool for the Identification of Delirium Risk in Older In-Patients: A Case-Control Study. *J. Clin. Nurs.* 2018, 27, 345–354. [CrossRef] [PubMed]

46. Zuliani, G.; Bonetti, F.; Magon, S.; Prandini, S.; Sioulis, F.; D’Amato, M.; Zampi, E.; Gasperini, B.; Cherubini, A. Subsyndromal Delirium and Its Determinants in Elderly Patients Hospitalized for Acute Medical Illness. *J. Gerontol. A Biol. Sci. Med. Sci.* 2013, 68, 1296–1302. [CrossRef]

47. Evensen, S.; Saltvedt, I.; Ranhoff, A.H.; Myrstad, M.; Myrstad, C.; Mellingsæter, M.; Wang-Hansen, M.S.; Neerland, B.E. Delirium and cognitive impairment among older patients in Norwegian emergency departments. *Tidsskr Nor Laegeforen* 2019, 139. [CrossRef]

48. Gonzalez, C.V.; Dupuy, J.-F.; López, M.F.; Luaces, P.L.; Rodriguez, C.R.; Marinello, G.G.; Vinagera, E.N.; Verdecia, B.G.; Brito, B.W.; Perez, L.M.; et al. Stratified Cox Regression Analysis of Survival under CIMAvax®EGF Vaccine. *JCT* 2013, 4, 8–14. [CrossRef] [PubMed]

49. Zhu, X.; Zhou, X.; Zhang, Y.; Sun, X.; Liu, H.; Zhang, Y. Reporting and Methodological Quality of Survival Analysis in Articles Published in Chinese Oncology Journals. *Medicine* 2017, 96. [CrossRef] [PubMed]

50. Eulenburg, C.; Schroeder, J.; Obi, N.; Heinz, J.; Seibold, P.; Rudolph, A.; Chang-Claude, J.; Flesch-Janys, D. A Comprehensive Multistate Model Analyzing Associations of Various Risk Factors with the Course of Breast Cancer in a Population-Based Cohort of Breast Cancer Cases. *Am. J. Epidemiol.* 2016, 183, 325–334. [CrossRef] [PubMed]

51. Begun, A.; Icks, A.; Waldeyer, R.; Landwehr, S.; Koch, M.; Giani, G. Identification of a Multistate Continuous-Time Nonhomogeneous Markov Chain Model for Patients with Decreased Renal Function. *Med. Decis. Mak.* 2013, 33, 298–306. [CrossRef]