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Association between Early Delirium and Treatment Limitation Decisions in Internal Medicine Patients

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Abstract

Deciding to limit treatment (TLD) is a complicated process influenced by patients' other medical conditions and cultural considerations. We hypothesized that delirium is associated with the issuance of TLD orders in hospitalized patients. To determine whether the proportion of patients with at least one TLD order differs between those who have delirium and those who do not, to identify which factors are linked to TLD orders, and to investigate how TLD and delirium relate to the 90-day chance of dying or being readmitted to hospital. Every patient admitted to the internal medicine ward of one hospital between November 2019 and January 2020 received a formal delirium assessment by a neuropsychologist within the first 48 hours of admission. Information on TLD orders, deaths within 90 days, and hospital readmissions was collected. The study included 217 patients. Of these, 119 (54.9%) had a "do not resuscitate" order, 107 (49.3%) had a "do not intubate" order, and 77 (35.5%) had a "do not admit to intensive care unit" order. Older age, higher Charlson comorbidity index, cognitive impairment, kidney failure, use of antidepressants or neuroleptics, and malnutrition were all linked to the presence of TLD orders. Patients with delirium were more likely to have at least one TLD order (24 out of 32 patients, 77.4%) than patients without delirium (95 out of 185 patients, 51.1%; OR = 3.3, 95%CI: 1.3-8.0; $p < 0.01$). After adjustment, this association was no longer statistically significant (aOR = 2.0; 95%CI: 0.7–5.6; $p = 0.20$). Having a TLD order (aHR = 1.8; 95%CI: 1.1–3.0) and having delirium (aHR = 1.8; 95%CI: 1.1–3.1) were both independently associated with a higher risk of death or hospital readmission within 90 days. Patients found to have delirium in the first 48 hours after hospital admission often receive orders limiting treatment. However, this relationship disappears once other medical conditions are taken into consideration.

Keywords: Delirium, Death, Hospital readmission, Treatment limitation decision, DNR

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Introduction

Delirium is a sudden disturbance in brain function characterized by fluctuating confusion, poor attention, and changes in level of consciousness [1]. In internal

medicine wards, its frequency ranges from 7% to 42% [1, 2]. The patients most likely to develop delirium are older adults, individuals taking many medications, people with substance use problems, those with existing neurocognitive disorders or neurologic illnesses, and patients who have had recent surgery or required intensive care unit admission [1]. Delirium places significant emotional strain on patients and their families [3, 4]. It is associated with worse outcomes, such as loss of independence, longer hospital stays, and higher overall healthcare costs [5]. Patients who arrive at emergency departments with delirium face a 70% higher chance of dying within 6 months, and the risk becomes 2 to 4 times greater when delirium develops in the intensive care unit [5].

Treatment limitation decisions (TLDs) are medical instructions that restrict the use of more aggressive therapies. They cover “do not resuscitate” (DNR), “do not intubate”, and “do not admit to intensive care unit” orders. Making these decisions is a complex process affected by the patient’s current illness, their ability to make choices, and the personal values of the patient, the doctor, or family members [6]. Greater age, multiple health problems, poor physical function, and neurocognitive deficits have all been associated with DNR orders in previous research [6, 7]. Because delirium usually points to a serious underlying health problem and commonly occurs together with advanced age or neurocognitive impairment, we hypothesized that patients experiencing delirium would more often have treatment limitation decisions documented at the time of hospital admission.

Our objective was to compare the proportion of patients with at least one TLD (i.e., DNR) order between those with and without delirium who were admitted to the internal medicine service, to describe which factors are associated with TLD orders, and to explore the link between DNR orders and the risk of hospital readmission or death within 90 days.

Materials and Methods

We conducted a secondary analysis of data from a prospective observational cohort study. The cohort consisted of patients admitted to the internal medicine unit of a secondary teaching hospital between 1 November 2019 and 6 January 2020 [8]. The primary purpose of the original study was to design an easy-to-use screening instrument capable of identifying delirium right at admission for individuals hospitalized in general internal medicine wards [8]. Details regarding TLD orders, along with any death or readmission within 90 days of the initial hospitalization, were systematically documented. Informed consent was collected directly from capable patients or, when capacity was lacking, from their legal representatives. The entire process complied with the standards of Good Clinical Practice and the Declaration of Helsinki. Ethical approval was granted by the Vaud Cantonal Ethics Committee (CER-VD). Preparation of the manuscript followed the recommendations outlined in the STROBE statement [9].

Participants

All adult individuals admitted to the Internal Medicine department during the specified timeframe were eligible for inclusion. Exclusion criteria included planned hospital stays of fewer than 3 days, inability to communicate in French, absence of a structured neuropsychological assessment, or the need for immediate life-saving emergency interventions.

Outcomes and measurements

The main outcome measured was the percentage of patients with at least one TLD order documented in their medical file (specifically, at least a DNR order). Additional outcomes focused on each of the three distinct TLD orders separately, the variables associated with those orders, the frequency with which delirium diagnoses were explicitly mentioned in clinical notes and discharge reports, and the combined endpoint of death or hospital readmission within 90 days.

A TLD order was recorded whenever any of the following appeared in the patient chart: “DNR”, “do not intubate”, and/or “do not admit to ICU”. These orders operated under a clear hierarchical structure whereby “do not intubate” automatically incorporated “DNR”, “do not admit to ICU” encompassed both preceding restrictions, and the detection of any TLD indicated the presence of at least a “DNR” order. The decision to restrict further treatment escalation was made following discussions among the patient, family members, and/or the attending physician.

Every participant received a dedicated 15–30-minute in-person evaluation by a neuropsychologist during the initial 48 hours following admission. This evaluation relied on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria, combined with the Confusion Assessment Method [10].

When the clinical presentation remained ambiguous, consensus was reached through consultation with two additional neuropsychologists. To ensure the treating physician remained unaware of the findings, the neuropsychologist conducted the assessment when the ward doctor was not present and adhered to strict instructions not to disclose any results to the clinical team.

Study-specific data collection occurred only once per patient after enrollment. All relevant information was retrieved from the hospital's digital patient files, including TLD orders, prior medical conditions, and currently prescribed medications. Overall comorbidity load was quantified using the Charlson Comorbidity Index (CCI).

Records of death or any hospital readmission occurring within 90 days of the index admission were extracted from the institution's electronic database. Because this facility serves as the sole public hospital for the entire region and manages nearly every admission locally, any stays in distant hospitals or private facilities could not be included in the dataset.

Statistics

Sample size determination was originally performed to develop a delirium screening tool, as detailed in an earlier report [8]. Using the final cohort of 217 patients, with an expected delirium rate of 15% and an alpha threshold of 5%, the retrospective power calculation showed more than 80% power to detect an absolute 30% difference in the rate of TLD orders between patients with and without delirium. In contrast, power fell below 60% for detecting a 20% absolute difference.

In the primary analysis, logistic regression was used, with the presence of any TLD order as the outcome and delirium status as the key predictor. Initial adjustments accounted for age (categorized at the median) and sex. Subsequent models additionally controlled for CCI (also split at the median), preexisting neurocognitive impairment, active oncologic disease, and chronic kidney disease (CKD), drawing on evidence from contemporary studies addressing treatment limitation practices [11]. Two separate sensitivity analyses were performed. The first stratification of delirium cases was based on whether the diagnosis had been formally recorded in the patient notes. The second step was to remove from the control group any patients who developed delirium at any point later during their hospitalization.

Given the hierarchical nature of the TLD orders, a secondary analysis employed ordinal logistic regression. Here, the ordered level of treatment limitation served as the outcome variable while delirium remained the main predictor. Adjustments mirrored those used in the primary model.

Exploratory analyses examined additional potential predictors of TLD orders (delirium excluded) through ordinal logistic regression adjusted only for age (at the median) and sex. Factor selection for these analyses was informed by prior literature [6, 7].

The raw association between having at least one TLD order (or delirium) and the 90-day composite endpoint of readmission or death was first assessed using Kaplan–Meier survival curves, with differences between groups evaluated via an unweighted two-sided log-rank test. Adjusted effects were then estimated with multivariate Cox regression models that incorporated median age, sex, median CCI, neurocognitive impairment, oncologic disease, and CKD [11]. Compliance with the proportional hazards assumption was confirmed both statistically via Schoenfeld residuals and visually through examination of log-minus-log survival plots.

Baseline patient characteristics were summarized using nonparametric methods, with medians and interquartile ranges reported. Between-group differences were tested with the chi-squared or Fisher's exact test for categorical data and the Mann-Whitney test for continuous variables when suitable. All statistical tests were two-sided, with a significance threshold of 5%. Analyses were executed using STATA version 17.0 (StataCorp LP, College Station, TX, USA).

Results and Discussion

Screening identified 253 potential candidates, of whom 217 were enrolled in the final analysis **(Figure 1).** Orders limiting treatment were common, as 119 patients (54.9%) received a DNR directive. Within this group of 119, 12 individuals (10.1%) had only the DNR order, 30 (25.2%) carried one extra restriction in the form of a "do not intubate" order, and the remaining 77 (64.7%) had the full set of two additional restrictions ("do not intubate" plus "do not admit to ICU"). A summary of patient features according to the presence or absence of treatment limitation decisions is presented in **Table 1**.

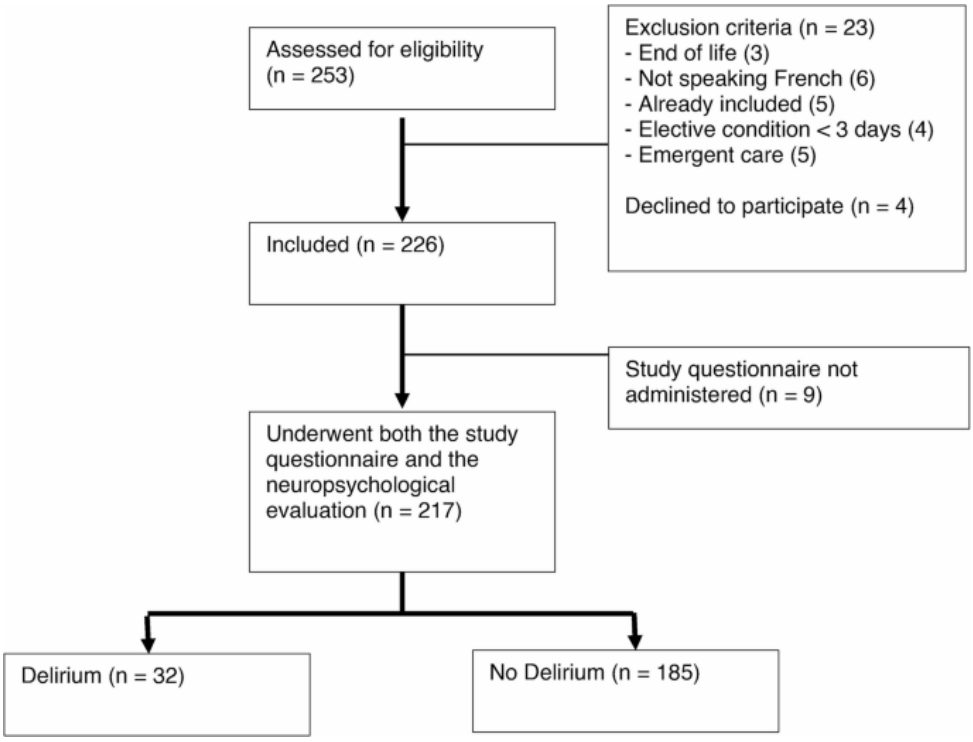

Figure 1. Study flowchart

Table 1. Characteristics of participants with and without treatment limitation decision (TLD). From: Treatment limitation decision in delirium: a secondary analysis of a prospective observational study

Variable	P-value	No TLD (n = 98)	Any TLD (n = 119)*	Total sample (n = 217)
Age (years), median (IQR)	< 0.01	67.9 (58.5–77.3)	83.4 (73.6–89.4)	75.9 (66.5–85.8)
Male sex	0.06	56 (57.1%)	53 (44.5%)	109 (50.2%)
Admission via the emergency department	0.01	88 (89.8%)	117 (98.3%)	205 (94.5%)
Non-smoker	0.03**	63 (64.3%)	89 (74.8%)	152 (70.0%)
Current smoker		27 (27.6%)	16 (13.4%)	43 (19.8%)
Former smoker		8 (8.2%)	14 (11.8%)	22 (10.1%)
Hypertension	0.02	55 (56.1%)	85 (71.4%)	140 (64.5%)
History of myocardial infarction	0.51	26 (26.5%)	27 (22.7%)	53 (24.4%)
Atrial fibrillation	0.01	20 (20.4%)	43 (36.1%)	63 (29.0%)
Peripheral arterial disease	0.81**	8 (8.2%)	11 (9.2%)	19 (8.8%)
Heart failure	0.03	33 (33.7%)	57 (47.9%)	90 (41.5%)
History of stroke	0.24	16 (16.3%)	27 (22.7%)	43 (19.8%)
Stroke without sequelae	0.44**	12 (12.2%)	18 (15.1%)	30 (13.8%)
Stroke with sequelae		4 (4.1%)	9 (7.6%)	13 (6.0%)
Cognitive impairment	< 0.01			
• Mild		13 (13.3%)	31 (26.3%)	44 (20.3%)
• Severe		7 (7.1%)	32 (26.9%)	39 (18.0%)
Diabetes mellitus	0.43**	26 (26.5.6%)	23 (19.3%)	49 (22.6%)
• Insulin-treated		10 (10.2%)	10 (8.4%)	20 (9.2%)
• Non-insulin-treated		16 (16.3%)	13 (10.9%)	29 (13.4%)
Chronic obstructive pulmonary disease (COPD)	0.74	19 (19.4%)	21 (17.6%)	40 (18.4%)
Cancer status	0.53			
• Without metastasis		15 (15.3%)	25 (21.0%)	40 (18.4%)

• With distant metastasis		13 (13.3%)	13 (10.9%)	26 (12.0%)
Solid tumors	0.47	23 (23.5%)	33 (27.7%)	56 (25.8%)
Lymphoma or leukemia	0.19**	7 (7.1%)	3 (2.5%)	10 (4.6%)
Mild liver disease	0.26**	11 (11.2%)	6 (5.0%)	17 (7.8%)
Severe liver disease		6 (6.1%)	7 (5.9%)	13 (6.0%)
Acute kidney injury (AKI)	0.01**			
• Stage 1		15 (15.3%)	38 (31.9%)	53 (24.4%)
• Stage 2		5 (5.1%)	5 (4.2%)	10 (4.6%)
• Stage 3		1 (1.0%)	4 (3.4%)	5 (2.3%)
Chronic kidney disease (CKD)	< 0.01**			
• Stage 0		83 (84.7%)	79 (66.4%)	162 (74.7%)
• Stage I		1 (1.0%)	0 (0%)	1 (0.5%)
• Stage II		1 (1.0%)	4 (3.4%)	5 (2.3%)
• Stage III		12 (12.2%)	22 (18.5%)	34 (15.7%)
• Stage IV		1 (1.0%)	14 (11.8%)	15 (6.9%)
• Stage V		–	–	–
Charlson comorbidity index, median (IQR)	< 0.01	3 (1–5)	4 (3–5)	3 (2–5)
Anemia	0.08	30 (30.6%)	50 (42.0%)	80 (36.9%)
Alcohol use	0.12**			
• Current		23 (23.5%)	15 (12.6%)	38 (17.5%)
• Former		7 (7.1%)	10 (8.4%)	17 (7.8%)
Psychiatric disorders	0.55	30 (30.6%)	41 (34.5%)	71 (32.7%)
Substance abuse	0.20**			
• Current		6 (6.1%)	3 (2.5%)	9 (4.1%)
• Former		3 (3.1%)	1 (1.0%)	4 (1.8%)
Rheumatologic conditions	< 0.01	22 (22.5%)	56 (47.1%)	78 (35.9%)
Malnutrition status	0.16**			
• Mild		8 (8.2%)	16 (13.5%)	24 (11.1%)
• Moderate		11 (11.2%)	20 (16.8%)	31 (14.3%)
• Severe		9 (9.2%)	16 (13.5%)	25 (11.5%)
Enteral feeding via nasal tube	0.73**	3 (3.2%)	5 (4.4%)	8 (3.8%)
Urinary incontinence	0.03	15 (15.2%)	33 (27.7%)	48 (22.1%)
Nocturia	0.25	43 (43.3%)	61 (51.3%)	104 (47.9%)
Urinary urgency	0.82	28 (28.3%)	32 (26.9%)	60 (27.6%)
Urinary catheter use	0.39**	9 (9.1%)	16 (13.5%)	25 (11.5%)
Pre-admission diuretic use	0.10	34 (34.3%)	54 (45.4%)	88 (40.5%)
Pre-admission opioid use	0.83**	26 (26.3%)	33 (27.7%)	59 (27.2%)
Pre-admission antipsychotic use	0.39	14 (14.1%)	22 (18.5%)	36 (16.6%)
Pre-admission antidepressant use	0.17	18 (18.2%)	31 (26.1%)	49 (22.6%)
Pre-admission benzodiazepine use	0.62	31 (31.3%)	41 (34.5%)	72 (33.2%)

1. Values are numbers (percentage) unless otherwise stated
2. AKI acute kidney injury, CKD chronic kidney disease by CKD-EPI classification, COPD chronic obstructive pulmonary disease, ER emergency room, TLD treatment limitation decision, UC urinary catheterization
3. * Presence of any TLD means at least an “DNR” order, ** Fischer test

Treatment limitation decision in delirium (primary outcome)

The neuropsychologist detected delirium in 14.3% of the cohort (95%CI: 9.6%−19.0%) during the first 48 hours after admission. Those diagnosed with delirium tended to be older and exhibited higher rates of prior myocardial infarction, existing neurocognitive problems, acute kidney injury episodes, history of stroke, psychiatric conditions, rheumatic illnesses, signs of malnutrition, use of neuroleptic drugs before admission, antidepressant use

before admission, insertion of a urinary catheter, and greater overall comorbidity burden as measured by the Charlson index.

Patients who had delirium showed a markedly higher rate of at least one treatment limitation decision (24 out of 32 patients, 77.4%) than those free from delirium (95 out of 185 patients, 51.1%, OR = 3.3; 95% CI: 1.3–8.0; P < 0.01). After accounting for age and sex alone, the relationship remained significant (aOR = 2.7; 95% CI: 1.1–7.2; P = 0.04). Once the model was further adjusted for age, sex, Charlson comorbidity index, neurocognitive impairment, oncologic disease, and chronic kidney disease, the association no longer reached statistical significance (aOR = 2.0; 95% CI: 0.7–5.6; P = 0.20).

Based on the intensity of restrictions, none of the delirium patients (0%) had exactly one order; 7 (22.6%) had two orders; and 17 (54.8%) had all three orders. In comparison, the non-delirium group had 12 (6.4%) with one order, 23 (12.4%) with two orders, and 60 (32.3%) with three orders (P < 0.01 overall). On an ordered scale, delirium was linked to a greater chance of progressing to more severe treatment restrictions (OR = 2.9; 95%CI: 1.4–6.0; p < 0.01). This stepwise difference lost significance after full adjustment (aOR = 1.6; 95% CI: 0.7–3.6; P = 0.34).

Sensitive analysis

Among patients diagnosed with delirium, the condition was explicitly recorded in the hospital notes for 64.5% (95% CI: 46.7–82.4%) and appeared in the discharge letter to the general practitioner for 58.1% (95% CI: 39.7%−76.5%). When delirium had been noted in the records, the link to at least one treatment limitation decision remained significant (OR 2.9; 95% CI: 1.1–8.2; P = 0.04). The association was weaker and non-significant for unrecognized cases (OR 4.3; 95% CI: 0.9–20.5; P = 0.07), as well as after full statistical adjustment (aOR 1.6; 95% CI: 0.5–5.4; P = 0.46).

A further sensitivity check removed the 13 control patients (7.0%) who developed delirium at any later stage of their stay. In this restricted sample, the odds ratio for having at least one TLD order stood at 3.4 (95% CI: 1.4–8.3; P < 0.01) before adjustment, 2.8 (95% CI: 1.1–7.5; P = 0.04) after age- and sex-adjustment, and 2.0 (95% CI: 0.7–5.9; P = 0.19) in the fully adjusted model.

Factors associated with TLD

Older age, along with cognitive impairment, was the strongest driver of the issuance of treatment limitation orders **(Table 2)**. When age and sex were controlled for, the Charlson comorbidity index, cognitive impairment, acute or chronic renal failure, pre-hospital use of neuroleptics or antidepressants, and malnutrition continued to show meaningful links with treatment limitation orders **(Table 2).**

Table 2. Factors associated with treatment limitation decision (TLD) in unadjusted and adjusted ordinal logistic regression. Results are odds ratios (95%CI) for having any greater limitation of treatment (e.g.: “no TLD” vs. “any TLD”, “no TLD or DNR” vs. “DNI or no ICU”, and “no TLD, DNR or DNI” vs. “no ICU”). From: Treatment limitation decision in delirium: a secondary analysis of a prospective observational study

Variable	OR adjusted for age and sex (95% CI)	Crude OR (95% CI)
General characteristics		
Age – Q2	2.8 (1.2–6.5)*	2.6 (1.2–6.1)*
Age – Q3	5.2 (2.3–11.8)*	5.0 (2.2–11.1)*
Age – Q4	12.9 (5.6–29.5)*	12.9 (5.7–29.6)*
Comorbidity profile		
CCI – Q2	1.6 (0.8–3.4)	1.8 (0.9–3.6)
CCI – Q3	1.9 (0.9–3.8)	2.3 (1.2–4.4)*
CCI – Q4	2.1 (1.0–4.6.0.6)*	2.2 (1.1–4.6)*
Diabetes mellitus	0.9 (0.5–1.8)	0.8 (0.4–1.4)
Hypertension	1.6 (0.9–2.9)	2.2 (1.3–3.8)*
Neurocognitive status		
Mild impairment	2.0 (1.0–4.1.0.1)*	3.3 (1.7–6.3)*
Severe cognitive impairment	3.2 (1.6–6.6)*	4.5 (2.3–8.9)*
Chronic kidney disease (CKD)	2.3 (1.2–4.4)*	3.4 (1.8–6.3)*
Psychiatric conditions	1.7 (0.9–3.1)	1.4 (0.8–2.4)
Rheumatologic disorders	1.8 (0.9–2.6)	2.8 (1.6–4.7)*

Admission-related factors		
Admission via the emergency department	8.2 (1.7–42.3)*	6.9 (1.5–31.9)*
Acute kidney injury (AKI)	1.8 (1.1–3.1)*	1.9 (1.1–3.3)*
Malnutrition	1.8 (1.0–3.1.0.1)*	1.8 (1.1–3.0.1.0)*
Oncologic comorbidity	1.3 (0.7–2.3)	1.1 (0.6–1.8)
Urinary incontinence (UI)	1.7 (0.9–3.1)	1.9 (1.1–3.4)*
Medication before admission		
Neuroleptic use	2.4 (1.1–5.0.1.0)*	1.9 (0.9–3.7)
Antidepressant use	2.1 (1.1–3.9)*	1.8 (1.0–3.3.0.3)

1. As these three orders were nested in ascending order, “do not intubate” implies “DNR”, and “do not admit to ICU” includes the first two orders.
2. UI urinary incontinence, AKI acute kidney injury, ER emergency room, CKD chronic kidney disease, LD liver disease, COPD chronic obstructive pulmonary disease, CI cognitive impairment, PAD peripheral arterial disease, MI myocardial infarct, HBP high blood pressure, CCI Charlson comorbidity index, Q1-4 first to fourth quartile, DNR do not resuscitated, DNI do not intubate, No ICU do not admit to intensive care unit
3. *P-value < 0.05
90-day hospital readmission or death.

In the 90 days after admission, 34 patients (15.7%) had died, and 61 patients (28.4%) had been readmitted to the hospital on at least one occasion. Without adjustment, the hazard ratio for the combined outcome of readmission or mortality was 2.2 (95% CI: 1.3–3.6) for patients with delirium and 2.0 (95% CI: 1.3–3.2) for those with at least one treatment limitation order. These links held firm in the fully adjusted models that mutually controlled for one another, producing hazard ratios of 1.8 (95% CI: 1.1–3.1) for delirium and 1.8 (95% CI: 1.1–3.0) for having at least one TLD order. The highest risk was among patients who had both delirium and at least one treatment limitation order, compared with those free of any limitation orders (aHR 3.6; 95% CI: 2.0–6.7; P < 0.001). An intermediate risk was observed in patients with treatment limitation orders without delirium (aHR 1.6; 95% CI: 0.9–2.8; P = 0.08); **(Figure 2).**

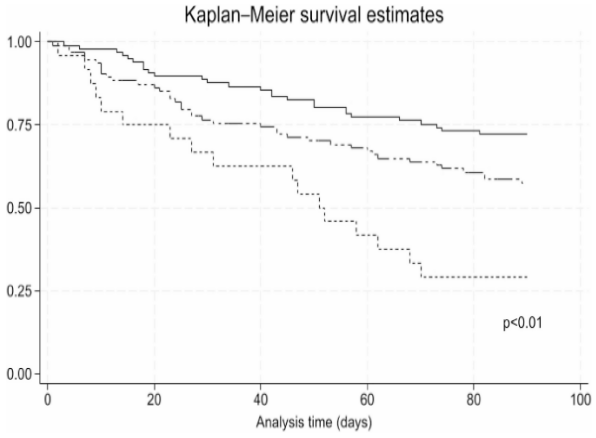

Figure 2. Treatment limitation decision in delirium: a secondary analysis of a prospective observational study

Time to hospital readmission or death. **Figure 2** represents patients without treatment limitation decision (solid line), patients with treatment limitation decision but no delirium (dashed line), and patients with treatment limitation decision and delirium (dotted line)

Patients found to have delirium in the first 48 hours after admission showed a strong likelihood of having treatment limitation orders, with such orders recorded in three-quarters of their medical records. Although this rate was noticeably higher than in patients without delirium (where half had TLD orders), the difference largely disappeared once comorbidities linked to delirium—primarily neurocognitive impairment—were taken into account.

Age emerged as the factor most strongly linked to all treatment limitation orders. Interestingly, active cancer was not associated with TLD, while neuro-psychiatric conditions (including delirium, cognitive impairment, and the use of neuroleptics or antidepressants) showed strong associations. This pattern contrasts with findings from 30 years ago in a meta-analysis of factors related to DNR orders, in which the odds ratio for cancer (OR 2.6; 95% CI 2.1–3.2) was twice that for cognitive impairment (OR 1.2; 95% CI 1.1–1.2) [6]. This shift may reflect the expanded range of treatment options and better quality of life now available to oncology patients. At the same time, it draws attention to the significant burden carried by individuals with psychiatric or neurocognitive disorders and their families. These observations emphasize the importance of routinely discussing personal values and

treatment limitation decisions with all admitted patients, including those with metastatic disease (except in cases of very limited life expectancy).

Individuals who experienced delirium and/or had at least one TLD faced an elevated risk of 90-day hospital readmission or death when compared with patients without any TLD. This finding aligns with the majority of earlier research on pre-admission [12], admission [13], and pre-operative advanced directive orders [14]. Because several relevant comorbidities (such as psychiatric illness or malnutrition) were not incorporated into the multivariate model, residual confounding may have influenced the results [2]. Nevertheless, prior studies support the presence of a true underlying association. For example, in patients undergoing planned surgery, those with DNR orders experienced higher mortality despite comparable rates of complications, resuscitations, intubations, or repeat procedures relative to a matched group [14]. Similarly, among older adults admitted for heart failure, myocardial infarction, pneumonia, stroke, or hip fracture, individuals with DNR orders displayed substantially higher mortality than would have been expected based on their admission demographic and clinical profile [13]. In yet another investigation involving propensity score-matched cohorts of vascular surgery patients who differed solely in DNR status, perioperative mortality stayed markedly higher in the DNR group (21% vs. 13%) [15]. Collectively, these results suggest that TLD orders, especially when accompanied by delirium, may serve as an independent sign of reduced health expectations [16], greater frailty [14], or diminished quality of care [13]—effects not fully accounted for by age or documented comorbidities.

The present study is subject to several limitations. First, it was conducted at a single center within one department (internal medicine), so the findings may not apply to other clinical environments. Second, the analysis of factors linked to TLD was exploratory. Decisions about treatment limitations involve a multifaceted process that includes patients, their families, and the responsible physician. The study did not aim to investigate the individual motivations behind these choices, an aspect that would be more suitably addressed through dedicated qualitative research. For these reasons, any interpretation of the factors associated with TLD orders should be approached cautiously. In addition, although the recorded date of the TLD order matched the admission date, the precise moment the decision was made remains unknown and may have occurred before hospitalization. This possible reversal in timing between delirium onset and TLD placement undermines the assumption of a direct causal relationship. Third, due to the observational design, it was not possible to adjust for all potential unmeasured confounders. However, the identified confounders were sufficient to eliminate the statistical significance of the link between delirium and TLD orders, and including additional variables would likely have produced little additional change. Lastly, the relatively small sample size, combined with a lower-than-anticipated prevalence of delirium, reduced the study's statistical power and limited the number of variables that could be included in the adjustment models.

Treatment limitation orders occur frequently among patients with delirium. These orders are linked, among other elements, to neuro-cognitive conditions. After adjustment for confounding factors, the relationship between delirium and TLD orders lost statistical significance. Patients who have both treatment limitation orders and delirium carry a substantially elevated risk of 90-day hospital readmission or death.

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Conflict of Interest: None

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Ethics Statement: These procedures followed the precepts of Good Clinical Practice and the Helsinki Declaration. The study was approved by the Vaud Cantonal Ethics Committee (CER-VD). Consent was obtained from patients or their next of kin if they were unable to give consent.

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