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ORIGINAL COMMUNICATION

Is pre-existing dementia an independent predictor of outcome after stroke? A propensity score-matched analysis

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Abstract With an aging population, patients are increasingly likely to present with stroke and pre-existing dementia, which may lead to greater death and disability. The aim of this work was to assess the risk of all-cause mortality and poor functional outcomes after ischemic stroke in patients with and without pre-existing dementia. We conducted a multicenter cohort study of all patients presenting to 12 tertiary care institutions participating in the Registry of the Canadian Stroke Network (RCSN) with a first ischemic stroke between 2003 and 2008. Individuals with pre-existing dementia were matched using propensity-score methods with patients without dementia during their index hospitalization based on the following characteristics: age (within 3 years), sex, stroke severity, stroke subtype (lacunar vs. non-lacunar), level of consciousness, vascular risk factors, dysphagia, glucose and creatinine on admission, Charlson index, residence prior to hospitalization (home vs. other), pre-admission dependency, hospital arrival via ambulance, admission to stroke unit, thrombolysis, and palliative care. A propensity score for all-cause mortality and clinical outcomes was developed. Registry of the Canadian Stroke Network (RCSN) and Registered Persons Database (RPDB). The primary outcome was all-cause mortality at 30 days. Secondary

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outcomes included mortality at discharge and at 1 year, disability at discharge (modified Rankin scale $\geq$ 3), medical complications (pneumonia), and discharge disposition. A subgroup analysis assessing the risk of intracerebral hemorrhage among those receiving thrombolysis was also conducted. We matched 877 patients with an acute ischemic stroke and pre-existing dementia to 877 stroke patients without dementia. Patients were well matched. The mean age was 82 years and 58 % were women. Mortality at discharge, 30 days, and 1 year after stroke was similar in patients with and without dementia [for mortality at discharge RR 0.88 [95 % confidence interval (CI) 0.74–1.05]; mortality at 30-days: RR 0.88 (95 % CI 0.75–1.03) and mortality at 1 year: RR 1.01 (95 % CI 0.92–1.11). Patients with pre-existing dementia had similar disability at discharge and home disposition. In the subgroup of patients who received thrombolysis, there were no differences between those with and without dementia in the risk of intracerebral hemorrhage (RR 1.27; 95 % CI 0.69–2.35) and no differences in mortality or disability at discharge. Pre-existing dementia is not independently associated with mortality, disability, or institutionalization after ischemic stroke. Pre-existing dementia may not necessarily preclude access to thrombolytic therapy and specialized stroke care.

Keywords Stroke · Dementia · Elderly · Outcomes · Mortality · Thrombolysis · Alteplase · Mortality · Pneumonia · Disability

Introduction

Stroke is a devastating medical condition, whose effects may be compounded by pre-existing dementia. The risk of stroke and dementia both increase with age, and, over the next several decades, a greater number of clinicians and caregivers are expected to face the challenge of both conditions presenting together [1–5].

In Canada, over one-third of patients hospitalized for an acute ischemic stroke are 80 years of age or older [2]. According to a recent report, the worldwide costs of dementia will exceed 1 % of global gross domestic product in 2010, estimated at 604 billion USD in physician services, hospital costs, lost wages, and decreased productivity [6, 7].

Previous studies suggest that dementia may be a determinant of both death and poor functional outcomes after stroke [8, 9]. As a result, different paradigms of care (comprehensive assessment vs. case-by-case-based approach) for stroke patients with dementia have been under intense debate [10, 11]. Access to specialized stroke care (i.e., stroke unit admission, thrombolysis, stroke team assessment) is considered crucial in the provision of a high quality of care. On the other hand, there may be an inclination to minimize interventions in older patients with pre-existing dementia, especially if these interventions are not likely to substantially alter outcomes [2], and some studies have reported reduced use of coronary care units, neuroimaging, antibiotics, and feeding tubes in stroke patients with dementia [10, 12]. Organized inpatient stroke care including stroke unit admission and use of thrombolysis can reduce death and disability irrespective of age, stroke severity, and subtype [15–17]. However, it is not clear whether these benefits extend to patients with pre-existing dementia.

Unfortunately, there is little reliable information on whether dementia in itself is associated with an increased incident risk of death and dependency after an acute ischemic stroke.

In this study, our aims were to: (1) determine if pre-existing dementia is an independent predictor of all-cause mortality and disability after ischemic stroke, and (2) to conduct a subgroup analysis to evaluate clinical outcomes after thrombolytic therapy in matched cohorts of ischemic stroke patients with and without dementia.

Participants and methods

We conducted a retrospective, observational study, using the Registry of the Canadian Stroke Network (RCSN), a clinical database that includes patients who have experienced an acute stroke and admitted to participating institutions [18].

Participants were eligible if they were older than 18 years and admitted to any of 12 regional stroke centers in one of the largest province (Ontario) in Canada with a first acute ischemic stroke between July 2003 and September 2008 (see patient flow chart–supplemental file). Patients with transient ischemic attacks or hemorrhagic strokes were not included in this study since they have different underlying mechanisms, risk factors, and prognosis.

The RCSN, was established in 2001, with over 40,000 patients accrued. In its current phase, data are collected on all consecutive patients with stroke or transient ischemic attack seen in the emergency room or admitted to any of 12 participating stroke centers. The goal of the RCSN is to measure and monitor the quality of hospital stroke care delivery. Clinical data was collected at admission and discharge by neurology research nurses using chart abstraction. Details of the methodology used by the RCSN (www.rcsn.org), data quality and the definitions have been well described in previous publications [2]. All facilities included in this study are considered comprehensive or primary stroke centers as per the recommendations from the Brain Attack Coalition [19].

Baseline characteristics

Demographic characteristics, marital status, living status, and comorbid conditions were available through the RCSN. Stroke severity was assessed on admission using the validated Canadian Neurological Scale (CNS); higher scores using this scale indicate lower severity [20, 21]. Stroke severity was categorized as: mild (CNS > 8), moderate (CNS 5–7), or severe (CNS < 4). Patients were classified as either being admitted to a general ward or a stroke unit, defined as a designated ward where stroke care was provided by a multidisciplinary team. Ischemic stroke subtype was classified as small vessel disease, cardioembolic, large artery atherosclerotic disease, or undetermined based on documentation by the treating physician and the investigations recorded in the chart [2]. Patients who were able to complete all activities of daily living in the 3 months prior to the stroke event were classified as independent. Place of residence prior to admission was classified as home, rehabilitation facility, nursing home, retirement home, or undetermined ($n = 27$; 0.3 %).

Data quality

Chart validation studies have shown good to excellent agreement with the RCSN database, with kappa scores of >0.8 for key variables (age, sex, stroke type, thrombolysis use, comorbid conditions) (RCSN report; www.rcsn.org) [18].

Ethics and patient consent

Ethics approval was obtained from the St. Michael's Hospital institutional review board. The RCSN has the designation of a "prescribed registry", thereby allowing the collection of patient-level information without consent for the purpose of facilitating the provision of stroke care in Ontario.

Definition of dementia

Pre-existing dementia was defined as any type of dementia (degenerative, vascular, mixed) that was identified prior to the index stroke. It includes a chronic loss of mental function or slow, progressive, mental decline for at least 1 month, identified from clinical records, history/physical examination, or on the physician's admission notes.

Outcome measures

The primary outcome measure was all-cause mortality at 30 days.

Secondary outcomes included death at discharge and at 1 year, disability at discharge, pneumonia, and discharge disposition. Disability at discharge was assessed using the modified Rankin scale (mRS ≥ 3). Stroke-associated pneumonia required radiographic confirmation and development within the first 30 days after stroke.

A pre-specified subgroup analysis was conducted to determine death, disability, and the risk of intracerebral hemorrhage (ICH) for those receiving thrombolysis among those with and without dementia.

Analytical approach

Chi-square tests were used to compare categorical variables; ANOVA or Kruskal–Wallis tests were used to compare mean and median differences for continuous variables in baseline characteristics.

To account for differences in baseline characteristics, we used propensity-score methods to match patients with pre-existing dementia to those patients without pre-existing dementia [22, 23]. This approach would allow determining whether pre-existing dementia is an independent predictor of outcomes, or alternatively the associated comorbidities explained the poorer outcomes in these patients. The clinical variables of interest that were used in the propensity-score model were age, sex, stroke severity, stroke subtype (lacunar vs. other), hypertension, diabetes, hyperlipidemia, atrial fibrillation, previous stroke or TIA, level of consciousness on arrival, dysphagia, glucose and creatinine levels on admission, arrival to hospital from a residence (home vs. other), pre-admission dependency, palliative care, stroke unit admission, thrombolysis, physiotherapy, and arrival by ambulance. A matching algorithm was then used to match patients with pre-existing dementia and those without dementia within a caliper of 0.2 standard deviations of the logit of the propensity score, with matching ratio of 1:1. To determine whether the propensity-score approach achieved balance in potential confounders, we compared the proportions of each covariate considered in the multivariable risk adjustment model between patients with and without dementia [22]. Evidence of imbalance in potential confounders was identified by examining the reduction in absolute standardized differences (Tables 1, 2). Adequate balance was defined as a standardized difference less than 0.1 [24].

For all-cause mortality, 877 patients with pre-existing dementia were matched with 877 patients without dementia. Differences in baseline characteristics after matching are shown in Table 1.

For the analysis of outcomes after thrombolytic therapy ($n = 1{,}668$ including 101 patients with pre-existing

Table 1 Baseline characteristics of patients with and without dementia

	Original study cohort[a]				Matched cohort[a]			
	No dementia *n* (%)	Dementia *n* (%)	Standardized difference	*p* value	No dementia *n* (%)	Dementia *n* (%)	Standardized difference	*p* value
Total patients, total *N*	9,692 (90.9)	966 (9.1)	–	–	877 (50)	877 (50)	–	–
Age (years), mean ± SE	71.18 ± 14.16	82.42 ± 8.45	0.82	<0.001	82.30 ± 8.83	82.07 ± 8.43	0.03	0.58
Sex								
Female	4,546 (46.9)	582 (60.2)	0.27	<0.001	498 (56.8)	519 (59.2)	0.05	0.31
Charlson index	1.54 ± 2.12	3.03 ± 2.33	0.7	<0.001	2.97 ± 2.93	2.98 ± 2.28	0	0.956
CNS score, total	7.87 ± 3.04	6.28 ± 3.12	0.52	<0.001	6.46 ± 3.26	6.32 ± 3.10	0.04	0.359
LOC on arrival								
Alert	8,433 (87.0)	707 (73.2)	0.4	<0.001	664 (75.7)	656 (74.8)	0.02	0.658
Dysphagia	910 (9.4)	144 (14.9)	0.19	<0.001	120 (13.7)	124 (14.1)	0.01	0.783
Hypertension	6,559 (67.7)	674 (69.8)	0.04	0.183	614 (70.0)	614 (70.0)	0	1
Diabetes	2,436 (25.1)	271 (28.1)	0.07	0.047	246 (28.1)	247 (28.2)	0	0.958
Hyperlipidemia	3,379 (34.9)	244 (25.3)	0.2	<0.001	225 (25.7)	224 (25.5)	0	0.956
Angina/CAD	2,164 (22.3)	261 (27.0)	0.11	<0.001	264 (30.1)	239 (27.3)	0.06	0.187
Current smoker	2,005 (20.7)	71 (7.3)	0.34	<0.001	88 (10.0)	67 (7.6)	0.08	0.077
Atrial fibrillation	1,652 (17.0)	255 (26.4)	0.24	<0.001	234 (26.7)	230 (26.2)	0.01	0.829
Previous stroke/ TIA	2,991 (30.9)	475 (49.2)	0.39	<0.001	439 (50.1)	428 (48.8)	0.03	0.599
Glucose on admission (mmol/dl)	7.74 ± 3.42	7.79 ± 3.49	0.01	0.72	7.76 ± 3.15	7.78 ± 3.51	0.01	0.912
Creatinine on admission (μmol/l)	101.67 ± 64.71	109.97 ± 80.71	0.13	<0.001	112.51 ± 70.76	110.08 ± 82.80	0.03	0.509
Arrival from home versus other	7,624 (78.7)	538 (55.7)	0.55	<0.001	526 (60.0)	508 (57.9)	0.04	0.382
Preadmission status								
Independent	8,166 (84.3)	279 (28.9)	1.48	<0.001	264 (30.1)	268 (30.6)	0.01	0.835
Palliative care	1,090 (11.2)	264 (27.3)	0.49	<0.001	226 (25.8)	225 (25.7)	0	0.956
Stroke type								
Lacunar versus other	1,489 (15.4)	143 (14.8)	0.02	0.645	124 (14.1)	133 (15.2)	0.03	0.543
Admission to stroke unit	5,308 (54.8)	500 (51.8)	0.06	0.074	440 (50.2)	458 (52.2)	0.04	0.39
Thrombolysis	1,567 (16.2)	101 (10.5)	0.16	<0.001	101 (11.5)	99 (11.3)	0.01	0.881
Physiotherapy	8,198 (84.6)	810 (83.9)	0.02	0.547	749 (85.4)	746 (85.1)	0.01	0.84
Arrival by ambulance	7,008 (72.3)	854 (88.4)	0.37	<0.001	780 (88.9)	777 (88.6)	0.01	0.821

[a] Values in parenthesis are column percentages, unless indicated otherwise

dementia), there were 99 patients with dementia matched with 99 patients without dementia. Differences in baseline characteristics are presented in Table 2.

In the final propensity-score matched sample, paired *t* test (continuous variables) and McNemar test (binary variables) were used to compare outcomes. We calculated the adjusted RR in the original study cohort using the multivariable Poisson regression model. Results are reported as adjusted relative risk (RR) with the corresponding 95 % confidence intervals (95 % CI).

Statistical analysis was performed using SAS statistical software version 9.2.2 (SAS Institute Inc., Cary, NC). All

Table 2 Characteristics of dementia and no dementia patients receiving thrombolytic therapy

	Original study cohort[a]				Matched cohort[a]			
	No dementia *n* (%)	Dementia *n* (%)	Standardized difference	*p* value	No dementia *n* (%)	Dementia *n* (%)	Standardized difference	*p* value
Total patients, total *N*	1,567 (93.9)	101 (6.1)	–	–	99 (50)	99 (50)	–	–
Age (years) mean ± SD	71.00 ± 13.98	81.32 ± 7.40	0.75	<0.001	83.16 ± 7.52	81.29 ± 7.46	0.25	0.081
Sex (female)	739 (47.2)	67 (66.3)	0.39	<0.001	63 (63.6)	65 (65.7)	0.04	0.766
Charlson index								
Mean ± SD	1.30 ± 2.00	2.99 ± 1.99	0.85	<0.001	2.90 ± 2.73	2.95 ± 1.97	0.02	0.881
Median (IQR)	1 (0–2)	2 (2–4)	0.85	<0.001	2 (1–4)	2 (2–4)	0.02	0.191
CNS score, total								
Mean ± SD	5.86 ± 2.47	5.74 ± 2.66	0.05	0.657	5.27 ± 2.58	5.81 ± 2.65	0.2	0.151
Median (IQR)	6 (4–8)	6 (4–8)	0.05	0.575	5 (3–7)	6 (4–8)	0.2	0.124
LOC on arrival								
Alert	1,305 (83.3)	77 (76.2)	0.19	0.069	70 (70.7)	77 (77.8)	0.16	0.255
Dysphagia	148 (9.4)	15 (14.9)	0.18	0.076	14 (14.1)	14 (14.1)	0	1
Hypertension	1,031 (65.8)	79 (78.2)	0.26	0.01	74 (74.7)	77 (77.8)	0.07	0.616
Diabetes	292 (18.6)	31 (30.7)	0.31	0.003	36 (36.4)	30 (30.3)	0.13	0.366
Hyperlipidemia	556 (35.5)	37 (36.6)	0.02	0.815	40 (40.4)	36 (36.4)	0.08	0.559
Coronary artery disease	356 (22.7)	37 (36.6)	0.33	0.001	36 (36.4)	36 (36.4)	0.00	1.00
Current smoking	292 (18.6)	7 (6.9)	0.31	0.003	≤5	7 (7.1)	0.13	0.352
Atrial fibrillation	278 (17.7)	28 (27.7)	0.26	0.012	26 (26.3)	28 (28.3)	0.05	0.75
Previous stroke/ TIA	355 (22.7)	50 (49.5)	0.63	<0.001	45 (45.5)	48 (48.5)	0.06	0.669
Glucose on admission (mmol/dl)								
Mean ± SD	7.50 ± 2.79	7.98 ± 3.23	0.17	0.095	8.26 ± 3.06	7.92 ± 3.22	0.11	0.45
Median (IQR)	7 (6–8)	7 (6–9)	0.17	0.228	7 (6–9)	7 (6–9)	0.11	0.18
Creatinine on admission (μmol/l)								
Mean ± SD	100.47 ± 51.93	111.92 ± 98.54	0.2	0.046	115.78 ± 54.36	112.73 ± 99.37	0.04	0.789
Median (IQR)	91 (77–110)	97 (80–120)	0.2	0.064	103 (84–125)	98 (82–121)	0.04	0.208
Arrival to hospital								
Home versus other	1,139 (72.7)	59 (58.4)	0.32	0.002	60 (60.6)	59 (59.6)	0.02	0.885
Preadmission status								
Independent	1,439 (91.8)	49 (48.5)	1.48	<0.001	55 (55.6)	49 (49.5)	0.12	0.393
Palliative care	215 (13.7)	27 (26.7)	0.37	<0.001	32 (32.3)	27 (27.3)	0.11	0.437
Stroke type								
Lacunar versus other	110 (7.0)	8 (7.9)	0.04	0.732	6 (6.1)	7 (7.1)	0.04	0.774
Admission to stroke unit	594 (37.9)	41 (40.6)	0.06	0.59	39 (39.4)	41 (41.4)	0.04	0.772
Physiotherapy	1,381 (88.1)	93 (92.1)	0.12	0.23	93 (93.9)	91 (91.9)	0.08	0.579
Arrival by ambulance	1,477 (94.3)	97 (96.0)	0.08	0.451	95 (96.0)	95 (96.0)	0	1

[a] Values in parenthesis are column percentages, unless indicated otherwise. Cells with numbers below 5 are not reported to preserve confidentiality

tests were two-tailed, and p values <0.05 were considered significant.

Results

Among 10,658 eligible patients with an acute ischemic stroke, 966 (9.1 %) had pre-existing dementia. Patients with pre-existing dementia were older (82 vs. 71 years; $p < 0.001$), and had more severe strokes (mean CNS score 7.9 vs. 6.3; $p < 0.001$). Diabetes, atrial fibrillation, coronary artery disease, and prior stroke/TIA were more prevalent in patients with dementia, whereas hyperlipidemia and smoking were more commonly found in patients without dementia. From the entire cohort, 877 (91 %) stroke patients with pre-existing dementia were matched with 877 stroke patients without dementia. Table 1 summarizes differences in baseline characteristics between groups before and after matching. There were no significant differences in baseline characteristics between patients with and without dementia in the matched cohort.

Overall, 1,668 (15.6 %) patients received thrombolytic therapy. Among patients with pre-existing dementia, 101 (10.5 %) received thrombolytic therapy, and 99 (98.0 %) of these were matched with 99 patients without dementia (Table 2).

Clinical outcomes

The main clinical outcome measures are summarized in Table 3 and Fig. 1.

Unmatched entire cohort

Unadjusted analyses of the unmatched cohort suggested lower survival at all points in time in patients with dementia compared to those without (Table 3). Similar findings were observed for death at discharge and at 1 year after stroke (Table 3). However, adjusted analyses revealed non-significant differences.

In an unadjusted analyses, disability at discharge, using the modified Rankin Scale (mRS), was higher in patients with dementia as compared to patients with no dementia (81.4 vs. 61.0 %; $p < 0.001$ for mRS 3–6) (Fig. 1). Patients with pre-existing dementia coming from home were less likely to be discharged home compared to patients without dementia (18.7 vs. 40.5 %) (Table 3). In addition, stroke patients with dementia appeared to be more likely to develop pneumonia (10.5 vs. 6.4 %; $p < 0.001$). Patients with dementia had longer mean length of hospital stay (LOS). However, adjusted analyses demonstrated no significant differences in any of these outcomes (Table 3).

Table 3 Outcome event rates in the original and matched cohorts

	Original study cohort (n = 10,658)			Matched cohort (n = 1,754)		
	Dementia	No dementia	RR from Poisson regression (95 % CI)	Dementia	No dementia	RR for propensity-matched cohort[a] (95 % CI)
Total no. of patients (%)	966 (9.1)	9,692 (90.9)		877 (50)	877 (50)	–
Main outcome measure						
30-day mortality (%)	254 (26.3)	1,187 (12.2)	0.96 (0.81–1.12)	217 (24.7)	247 (28.2)	0.88 (0.75 to 1.03)
Secondary outcomes						
Mortality at discharge (%)	208 (21.5)	1,080 (11.1)	0.93 (0.78–1.11)	182 (20.8)	207 (23.6)	0.88 (0.74 to 1.05)
1 year mortality (%)	465 (48.1)	2,128 (22.0)	0.97 (0.86–1.09)	414 (47.2)	410 (46.8)	1.01 (0.92 to 1.11)
Length of stay (mean ± SD), days	18.22 ± 30.42	14.43 ± 33.48	1.01 (1.00–1.03)	18.33 ± 31.41	19.56 ± 88.03	−1.28 (−7.5 to 4.9)[b]
Pneumonia	101 (10.5)	624 (6.4)	0.82 (0.64–1.04)	91 (10.4)	103 (11.7)	0.88 (0.68 to 1.14)
Disability at discharge (mRS 3–5)[c]	616 (63.8)	4,784 (49.4)	1.04 (0.95–1.15)	564 (64.3)	514 (58.6)	1.10 (1.02 to 1.19)
Discharge home[c]	181 (18.7)	3,927 (40.5)	0.88 (0.75–1.03)	172 (19.6)	170 (19.4)	1.01 (0.84 to 1.22)

Values in parenthesis are column percentages, unless indicated otherwise

[a] Propensity-matched sample (n = 877 with pre-existing dementia and n = 877 without dementia) matched on: age, sex, stroke severity, stroke subtype (lacunar vs. non-lacunar), hypertension, diabetes, hyperlipidemia, atrial fibrillation, previous stroke or transient ischemic attack, level of consciousness on arrival, dysphagia, glucose and creatinine levels on admission, place from arrival (home vs. other), pre-admission disability, palliative care, stroke unit admission, thrombolysis, physiotherapy, and arrival by ambulance. The RR of dementia versus non-dementia in the original study cohort (using multivariable Poisson regression model) were adjusted for the same variables used in the propensity matching (as described above)

[b] Paired t test for the mean between patients with and without pre-existing dementia in the propensity-matched cohort (p = 0.687)

[c] For disability/disposition at discharge, there were 672 patients with dementia matched with 672 patients without dementia who were discharged alive and available for the analysis

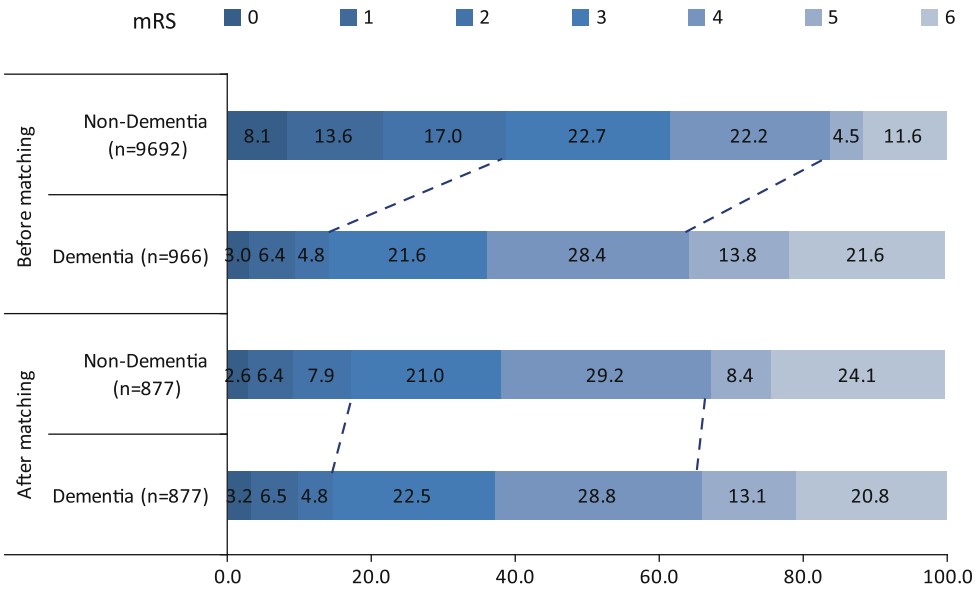

Fig. 1 Disability at discharge in stroke patients with and without pre-existing dementia before matching and after matching. This figure illustrates the disability at discharge according to the modified Rankin scale (mRS *0* no symptoms; *6* death) before and after propensity-score matching. The *dotted lines* show the corresponding category (mRS 0–2 and mRS 5–6) between patients with and without dementia. Before matching, there was a higher disability at discharge (mRS $\geq$ 3) among stroke patients with pre-existing dementia (p value <0.001). The differences disappeared after matching (RR 1.10, 95 % CI 0.96–1.27) for age, sex, stroke severity, stroke subtype (lacunar vs. non-lacunar), hypertension, diabetes, dyslipidemia, atrial fibrillation, previous stroke or transient ischemic attack, level of consciousness on arrival, dysphagia, glucose and creatinine levels on admission, place from arrival (home vs. other), pre-admission dependency, palliative care, stroke unit admission, thrombolysis, physiotherapy, and arrival by ambulance. Modified Rankin scale (mRS): *0* no symptoms, *1* no significant disability, able to carry out all usual activities, despite some symptoms; *2* slight disability, able to look after own affairs without assistance, but unable to carry out all previous activities; *3* moderate disability, requires some help, but able to walk unassisted; *4* moderately severe disability, unable to attend to own bodily needs without assistance, and unable to walk unassisted; *5* severe disability, requires constant nursing care and attention, bedridden, incontinent; *6* dead

Propensity-matched cohort

Similar to the adjusted analyses in the entire cohort, there were no differences in survival at 30 days (RR = 0.88, 95 % CI 0.75–1.03), at discharge (RR = 0.88, 95 % CI 0.74–1.05), or 1 year (RR = 1.01, 95 % CI 0.92–1.11) after stroke between patients with and without dementia (Table 3).

Disability at discharge was similar between patients with dementia and those without dementia (85.2 vs. 82.7 %) (Fig. 1). There was a slight increase in disability (RR = 1.10, 95 % CI 1.02–1.19) when only considering patients discharged alive (mRS 3–5) (Table 3). There were no significant differences in discharge to home, LOS, or risk of pneumonia between patients with and without pre-existing dementia (Table 3).

Clinical outcomes after thrombolytic therapy

In the original cohort, patients with pre-existing dementia were less likely to receive intravenous thrombolysis (10.5 vs. 16.2 %; $p < 0.001$) than their non-demented counterparts (Table 2).

Overall, 30-day mortality was higher among patients with dementia (26.7 vs. 16.9 %) in the unadjusted analysis, but the differences were not significant in the adjusted analysis (RR = 1.03, 95 % CI 0.67–1.60) (Table 4). Similarly, there were no significant differences in death or disability at discharge, disability at discharge, or disposition in the adjusted analysis in the original cohort. In the matched cohort, the risks of death, disability, and disposition after thrombolysis were similar in those with and without dementia. In addition, patients with and without pre-existing dementia had a comparable risk of ICH and neurological deterioration (Table 4).

Discussion

Stroke care for patients with pre-existing dementia represents a clinical challenge and may raise practical and ethical issues in management [3, 25]. Cerebral infarction is a risk factor for post-stroke dementia [2] and pre-stroke cognitive impairment or dementia itself can be associated with an increased risk of stroke [2]. The complex relationship between stroke and dementia is also known to have a pathological substrate: cortical or subcortical involvement after stroke in patients with Alzheimer pathology accelerates the clinical expression of dementia,

Table 4 Outcome measures among dementia and no dementia patients receiving thrombolytic therapy

	Original study cohort $n = 1{,}668$			Matched cohort $n = 198$		
	Dementia	No dementia	RR from Poisson regression (95 % CI)	Dementia	No dementia	Relative risk for propensity matched cohort[a] (95 % CI)
Total no. of patients (%)	101 (6.1)	1,567 (93.9)		99 (50)	99 (50)	–
Main outcome measures						
30-day mortality (%)	27 (26.7)	265 (16.9)	1.03 (0.67–1.60)	27 (27.3)	28 (28.3)	0.96 (0.60–1.55)
Intracerebral hemorrhage (any type within 36 h)	19 (18.8)	188 (12.0)	1.56 (0.92–2.63)	19 (19.2)	15 (15.2)	1.27 (0.69–2.35)
Symptomatic intracerebral hemorrhage	11 (10.9)	102 (6.5)	1.28 (0.63–2.60)	11 (11.1)	11 (11.1)	1.00 (0.47–2.13)
Secondary outcomes						
Neurological deterioration	11 (10.9)	107 (6.8)	0.96 (0.47–1.95)	11 (11.1)	12 (12.1)	0.92 (0.44–1.94)
Mortality at hospital discharge (%)	22 (21.8)	239 (15.3)	0.94 (0.58–1.52)	22 (22.2)	26 (26.3)	0.85 (0.51–1.41)
Death or disability at discharge	91 (90.1)	1,072 (68.4)	1.14 (0.90–1.45)	89 (89.9)	82 (82.8)	1.09 (0.98–1.22)
Disability at discharge (mRS 3–5)	69 (68.3)	824 (52.6)	1.25 (0.95–1.65)	67 (67.7)	55 (55.6)	1.22 (0.98–1.52)
Discharge home	14 (13.9)	480 (30.6)	0.75 (0.43–1.32)	14 (14.1)	11 (11.1)	1.27 (0.62–2.62)

Values in parenthesis are column percentages, unless indicated otherwise. The RR of dementia versus non-dementia in the original study cohort (using multivariable Poisson regression model) were adjusted for the same variables used in the propensity matching (as described above)

[a] Propensity-matched sample ($n = 99$ with pre-existing dementia and $n = 99$ without dementia) of patients receiving thrombolytic therapy matched for: age, sex, stroke severity, stroke subtype (lacunar vs. non-lacunar), hypertension, diabetes, hyperlipidemia, atrial fibrillation, previous stroke or transient ischemic attack, level of consciousness on arrival, dysphagia, glucose and creatinine levels on admission, place from arrival (home vs. other), pre-admission dependency, palliative care, stroke unit admission, thrombolysis, physiotherapy, and arrival by ambulance

affecting both the acute and chronic phase of stroke recovery [26]. There is continuing debate as to how to best manage stroke patients with pre-existing dementia. The lack of data on current processes and outcomes of care and the lack of established guidelines for the management and treatment of stroke patients with dementia contribute to this uncertainty.

In our study, we matched patients with and without pre-existing dementia presenting with an acute ischemic stroke and analyzed clinical and functional outcomes (e.g., disability at discharge and discharge home). We also evaluated outcomes and risks of intracerebral bleeding in a matched cohort of patients with and without dementia receiving thrombolytic therapy.

Patients with a history of dementia tended to be older women, had a higher prevalence of comorbid conditions (e.g., atrial fibrillation, and diabetes) and experienced more severe strokes. Although length of stay, disability, and mortality after stroke were all much higher in patients with dementia compared to those without in the overall sample, there was no significant difference in any of these outcomes in the propensity-matched cohort, suggesting that differences in outcomes after stroke are driven primarily by comorbid conditions rather than by dementia itself. In addition, among patients who received thrombolysis, there were no differences in rates of ICH, death, or disability between those with and without dementia.

In a previous descriptive study, we showed that patients with dementia were less likely to receive intravenous thrombolysis, even in the absence of recognized contraindications [27]. Differences in age, stroke severity, and overall frailty (e.g., disability, comorbidities) may explain why many clinicians decide not to treat these patients with thrombolysis. Excluding other medical reasons, contraindications were more common in patients with pre-existing dementia (13.5 vs. 7.5 %; $p < 0.001$). Herein, we showed similar clinical and functional outcomes for stroke patients receiving thrombolytic therapy with pre-existing dementia matched with those with no dementia. Interestingly, and despite the clinical perception, pre-existing dementia was not associated with a higher risk of ICH in the matched cohort.

Our study provides "real-world" information to address the question as to whether pre-existing dementia is an independent condition affecting clinical outcomes after ischemic stroke. Certainly, stroke patients with pre-existing dementia are frailer than their non-dementia counterparts. On average, patients with pre-stroke dementia were 11 years older and threefold more likely to be dependent than their non-dementia counterparts at the time of admission. Differences in demography, comorbidity, and disability make these patients highly vulnerable. For example, in the overall sample, death at 30 days or 1 year after stroke were twofold higher in patients with

pre-existing dementia compared to those without dementia (Table 3). Similarly, only 18.7 % of dementia patients were discharged home compared to 40.5 % without dementia. However, when these differences in patient demographics and comorbidities were accounted for, we observed no significant differences in clinical and functional outcomes (e.g., disability at discharge, disposition) between patients with pre-existing dementia and those without.

Altogether, these findings suggest that dementia in itself does not explain the observed poorer outcomes in unadjusted analysis. Rather, differences in patient baseline characteristics, stroke severity, and comorbid conditions may better explain these results. Accordingly, pre-existing dementia by itself should not necessarily limit access to thrombolytic therapy or to specialized care (e.g., stroke unit admission, ICU care).

There are some conflicting results in the literature about the individual mortality risk in patients with pre-existing dementia. Our findings differ from previous studies showing higher mortality or disability in patients with dementia [8, 9, 28]. The results of previous studies could be explained by the presence of confounders as observed in our original (unmatched) study cohort. More concisely, propensity-score matching is commonly used in observational studies that have groups with substantial differences in their baseline characteristics, similar to the process of randomization in clinical trials, where groups become more comparable after adjusting for confounders, thus differing only in the exposure to the treatment/intervention [29].

In other studies, differences in mortality were attenuated after adjusting for covariates [8, 28]. Medical complications and vascular death rather than dementia itself were the most common causes of death [28, 30]. These studies had multiple limitations, including small sample sizes (ranging between 202 and 453 patients), limited exposure (low number of patients with prestroke dementia, $n = 33$ to $n = 119$), low number of outcomes (total patient deaths were between 29 and 63), and analytic methods (lack of use of propensity matching to reduce residual confounding) [8, 9, 28, 30]. No information was provided on the risk of ICH or outcomes after thrombolytic therapy.

Consistent with our findings, a recently published case-control study using administrative databases found no significantly increased risk between patients with dementia and without dementia with respect to ICH (5.80 vs. 4.51 %; $p = 0.45$) or death (17.4 vs. 14.5 %; $p = 0.31$) [31].

Our study has both limitations and strengths. First, the main limitation relates to the definition of dementia pre-stroke, which does not follow a specific cognitive assessment or a scale of activities of daily living activities before stroke to evaluate dependency. Second, as we had no quantitative measure of cognition in patients with dementia, it is possible that patients with mild cognitive impairment or mild dementia were not appropriately identified. This is not an uncommon scenario in clinical practice, where individuals with mild cognitive impairment/dementia are not usually diagnosed until more advanced stages of the disease. Moreover, the similarities in death and disability at discharge as well as in the risk of intracerebral hemorrhage after thrombolysis is reassuring, as we most likely captured patients with moderate to severe dementia. Another limitation includes the scarce information on brain imaging. Finally, the analytical approach—propensity matching—would attenuate the possibility of residual confounding when analyzing different outcome measures.

Despite these limitations, our study shows that over 50 % of stroke patients with pre-existing dementia are alive at 1 year, and 80 % of those discharged alive had greater disability and had a need for institutionalization. However, it is not the dementia itself that explains these outcomes, but rather the associated comorbidities. Specifically, the higher prevalence of diabetes, atrial fibrillation, and previous stroke in conjunction with older age and more severe strokes make stroke patients with dementia more vulnerable. Interestingly, survival, disability and complications (e.g., ICH) after receiving thrombolysis are not different for patients with dementia compared to matched non-demented patients, suggesting that preexisting dementia per-se may not preclude access to thrombolytic therapy.

Some clinicians have reservations, and consequently are less likely to offer, more aggressive stroke care to elderly patients with pre-existing dementia. Our results provide a different perspective regarding the acute treatment, care, and management of stroke patients with concomitant dementia and as well may help clinicians in their treatment care decisions and in facilitating patient and/or family counseling or discussions. In some circumstances, therapeutic decisions should be made on the basis of stroke severity, associated comorbidities, or patient and families' preferences exclusive of the cognitive status.

Given the longer life expectancy in developed countries, the aging of the population, and recent discussions in health policy, this information will contribute to the ongoing debate pertaining to access to specialized care for this group of stroke patients. Representatives from governments, health care providers, and health insurers need to work together towards specific goals and priorities to facilitate access to stroke care and reduce the impact of stroke in this fragile population.

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Conflicts of interest None.

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