Albumin levels and risk of early cardiovascular complications after ischemic stroke: A propensity-matched analysis of a global federated health network

Tommaso Bucci, Daniele Pastori, Pasquale Pignatelli, George Ntaios, Azmil H. Abdul-Rahim, Francesco Violi & Gregory Y H Lip.

Supplemental Material

The TriNetX data are collected from member healthcare organizations (HCO) and originates from their primary electronic health records (EHR) system. A typical HCO is a large academic health center with data coming from majority of its affiliates. A single HCO frequently has more than one facility, including main and satellite hospitals. The data are stored on the TriNetX database via a physical server at the institution's data centre or a virtual hosted appliance. The TriNetX platform comprises of a series of these appliances connected into a federated network. This network can broadcast queries to each appliance. Results are subsequently collected and aggregated. Once the data are sent to the network, it is mapped to a standard and controlled set of clinical terminologies and undergoes a data quality assessment including 'data cleaning' that rejects records which do not meet the TriNetX quality standards. The TriNetX database performs internal and extensive data quality assessment with every refresh based on conformance, completeness, and plausibility (http://doi.org/10.13063/2327-9214.1244). HIPAA (Health Insurance Portability and Accountability Act) compliance of the clinical patient data is achieved using deidentification. Available data types within the network include demographics, diagnoses (represented by ICD-10-CM codes), procedures (coded in ICD-10-PCS or CPT), and measurements (coded to LOINC). While extensive information is provided about patients' diagnoses and procedures, other variables (such as socioeconomic and lifetime factors are not comprehensively represented). The advantage of electronic health record data over insurance claim data is that both insured and uninsured patients are included. An advantage of electronic health record data over survey data is that the former represents the diagnostic rates in the population presenting to healthcare facilities. This provides an accurate account of the burden of specific diagnoses on healthcare systems. One primary limitation of relying on diagnoses is that they do not account for undiagnosed patients who might have a condition but have not yet received medical support. Another general limitation of electronic health record data is that a patient may be seen in different HCO for different components of their care. If one healthcare organization is not part of the federated network, then part of their medical records may not be available. Using a network of healthcare organizations, rather than a single site, limits this possibility but does not fully remove it. Propensity Score Matched Analyses Using logistic regression [Logistic Regression of the scikit-learn package in Python (version 3.7)], TriNetX performs a 1:1 greedy nearest neighbor matching model, with a caliper of 0.1 pooled standard deviations. To eliminate bias resulting from nearest neighbor algorithms, the orders of rows are randomized. Any baseline characteristic with a standardized mean difference between cohorts lower than 0.1 is deemed well matched (https://www.tandfonline.com/doi/full/10.1080/00273171.2011.568786).

Table S1. ICD-10-CM codes for early cardiovascular complications.

Early cardiovascular complications	**ICD-10-CM-codes**
All-cause death	• Deceased (variable codified by TriNetX).
Acute myocardial infarction	• I21 Acute myocardial infarction
Atrial fibrillation	• I48 Atrial fibrillation and flutter
Ventricular arrhythmias	• I49.0 Ventricular fibrillation and flutter and/or • I47.2 Ventricular tachycardia
Heart failure	• I50 Heart failure
Takotsubo cardiopathy	• I51.81 Takotsubo syndrome

Table S2. Baseline characteristics, of stroke patients (without other possible causes of hypoalbuminemia) with reduced (cohort 1, n = 49,807) compared to normal (cohort 2, n = 232,965) albumin levels, before and after propensity score matching.

Demographics							
Cohort			Mean ± SD	Patients	% of Cohort	P-Value	Std diff.
1 2	Age	Age	72.8 +/- 14.2 70.8 +/- 14.7	49,807 232,965	100% 100%	<0.001	0.140
1 2	2106-3	White		32,233 154,251	64.7% 66.2%	<0.001	0.031
1 2	F	Female		24,756 112,023	49.7% 48.1%	<0.001	0.032
1 2	2054-5	Black or African American		10,727 43,501	21.5% 18.7%	<0.001	0.072
1 2	2028-9	Asian		1,043 5,743	2.1% 2.5%	<0.001	0.025
Diagnosis							
Cohort			Mean ± SD	Patients	% of Cohort	P-Value	Std diff.
1 2	I10-I16	Hypertension		35,542 118,228	71.4% 50.7%	<0.001	0.432
1 2	I20-I25	Ischemic heart diseases		17,166 46,435	34.5% 19.9%	<0.001	0.331
1 2	I48	Atrial fibrillation and flutter		12,050 29,033	24.2% 12.5%	<0.001	0.307
1 2	I50	Heart failure		12,043 25,886	24.2% 11.1%	<0.001	0.348
1 2	I26-I28	Pulmonary embolism		5,327 11,274	10.7% 4.8%	<0.001	0.220
1 2	E78	Dyslipidemia		26,502 93,022	53.2% 39.9%	<0.001	0.269
1 2	E08-E13	Diabetes mellitus		17,792 53,805	35.7% 23.1%	<0.001	0.280
1 2	E65-E68	Obesity		9,362 30,455	18.8% 13.1%	<0.001	0.157
1 2	N18	Chronic kidney disease		11,178 26,782	22.4% 11.5%	<0.001	0.295
1 2	I63	Cerebral infarction		35,986 79,321	72.3% 34.0%	<0.001	0.829
1 2	I73.9	Peripheral arterial disease		4,891 12,803	9.8% 5.5%	<0.001	0.163
Procedure							
Cohort			Mean ± SD	Patients	% of Cohort	P-Value	Std diff.
1 2	1013050	Echocardiography Procedures		21,312 54,894	42.8% 23.6%	<0.001	0.417
1 2	1013071	Cardiac Catheterization Procedures		4,050 9,981	8.1% 4.3%	<0.001	0.160
1 2	1013012	Electrocardiogram, routine ECG with at least 12 leads		31,735 89,367	63.7% 38.4%	<0.001	0.524
Medication							
Cohort			Mean ± SD	Patients	% of Cohort	P-Value	Std diff.
1 2	CV350	Antilipemic agents		28,950 94,734	58.1% 40.7%	<0.001	0.355
1 2	CV100	Beta blockers/related		26,886 79,167	54.0% 34.0%	<0.001	0.411
1 2	CV300	Antiarrhythmics		21,315 62,222	42.8% 26.7%	<0.001	0.343
1 2	CV700	Diuretics		20,268 63,217	40.7% 27.1%	<0.001	0.289

1 2	CV200	Calcium channel blockers		19,633 59,085	39.4% 25.4%	<0.001	0.304
1 2	CV800	ACE inhibitors		15,588 52,802	31.3% 22.7%	<0.001	0.195
1 2	CV805	Angiotensin ii inhibitor		8,971 31,912	18.0% 13.7%	<0.001	0.118
1 2	CV250	Antianginals		9,223 26,324	18.5% 11.3%	<0.001	0.204
1 2	BL110	Anticoagulants		29,474 76,908	59.2% 33.0%	<0.001	0.544
1 2	BL117	Platelet aggregation inhibitors		28,058 86,249	56.3% 37.0%	<0.001	0.395

Cohort 1 (N = 49,575) and cohort 2 (N = 49,575) characteristics after propensity score matching

Demographics

Cohort			Mean ± SD	Patients	% of Cohort	P-Value	Std diff.
1 2	Age	Age	72.8 +/- 14.2 72.6 +/- 14.1	49,575 49,575	100% 100%	0.030	0.014
1 2	2106-3	White		32,105 31,835	64.8% 64.2%	0.073	0.011
1 2	F	Female		24,628 24,867	49.7% 50.2%	0.129	0.010
1 2	2054-5	Black or African American		10,651 10,802	21.5% 21.8%	0.244	0.007
1 2	2028-9	Asian		1,037 1,009	2.1% 2.0%	0.532	0.004

Diagnosis

Cohort			Mean ± SD	Patients	% of Cohort	P-Value	Std diff.
1 2	I10-I16	Arterial hypertension		35,323 35,986	71.3% 72.6%	<0.001	0.030
1 2	I20-I25	Ischemic heart diseases		17,002 17,229	34.3% 34.8%	0.129	0.010
1 2	I48	Atrial fibrillation and flutter		11,908 11,888	24.0% 24.0%	0.882	0.001
1 2	I50	Heart failure		11,853 11,801	23.9% 23.8%	0.698	0.002
1 2	I26-I28	Pulmonary embolism		5,233 5,056	10.6% 10.2%	0.065	0.012
1 2	E78	Dyslipidemia		26,397 26,930	53.2% 54.3%	0.001	0.022
1 2	E08-E13	Diabetes mellitus		17,655 17,868	35.6% 36.0%	0.158	0.009
1 2	E65-E68	Obesity		9,308 9,462	18.8% 19.1%	0.212	0.008
1 2	N18	Chronic kidney disease		11,019 10,956	22.2% 22.1%	0.630	0.003
1 2	I63	Cerebral infarction		35,754 35,660	72.1% 71.9%	0.506	0.004
1 2	I73.9	Peripheral arterial disease		4,838 4,947	9.8% 10.0%	0.246	0.007

Procedure

Cohort			Mean ± SD	Patients	% of Cohort	P-Value	Std diff.
1 2	1013050	Echocardiography Procedures		21,128 21,650	42.6% 43.7%	0.001	0.021
1 2	1013071	Cardiac Catheterization Procedures		4,017 4,078	8.1% 8.2%	0.479	0.004
1 2	1013012	Electrocardiogram, routine ECG with at least 12 leads		31,504 32,391	63.5% 65.3%	<0.001	0.037

Medication							
Cohort			Mean ± SD	Patients	% of Cohort	P-Value	Std diff.
1 2	CV350	Antilipemic agents		28,806 29,289	58.1% 59.1%	0.002	0.020
1 2	CV100	Beta blockers/related		26,682 27,206	53.8% 54.9%	0.001	0.021
1 2	CV300	Antiarrhythmics		21,138 21,489	42.6% 43.3%	0.024	0.014
1 2	CV700	Diuretics		20,101 20,469	40.5% 41.3%	0.017	0.015
1 2	CV200	Calcium channel blockers		19,470 19,647	39.3% 39.6%	0.250	0.007
1 2	CV800	ACE inhibitors		15,500 15,870	31.3% 32.0%	0.012	0.016
1 2	CV805	Angiotensin ii inhibitor		8,942 9,117	18.0% 18.4%	0.150	0.009
1 2	CV250	Antianginals		9,153 9,365	18.5% 18.9%	0.084	0.011
1 2	BL110	Anticoagulants		29,247 29,917	59.0% 60.3%	<0.001	0.028
1 2	BL117	Platelet aggregation inhibitors		27,899 28,278	56.3% 57.0%	0.015	0.015

Table S3. Risk of primary and secondary outcomes in the sensitivity analyses.

	Reduced albumin events, n (%)	Normal albumin events, n (%)	HR (95%CI)
Patients aged >65 years n = 121,807 (each group)			
Composite outcome, n (%)	47,157 (38.7)	35,711 (29.3)	1.42 (1.40-1.44)
All-cause death, n (%)	17,711 (14.5)	7,216 (5.9)	2.62 (2.55-2.69)
Heart failure, n (%)	17,846 (14.7)	14,566 (12.0)	1.29 (1.26-1.32)
Atrial fibrillation, n (%)	23,055 (18.9)	21,670 (17.8)	1.11 (1.09-1.13)
Severe ventricular arrhythmias, n (%)	2,194 (1.8)	1,682 (1.4)	1.36 (1.28-1.45)
Myocardial infarction, n (%)	6,243 (5.1)	4,163 (3.4)	1.56 (1.50-1.62)
Takotsubo, n (%)	187 (0.2)	141 (0.1)	1.37 (1.10-1.71)
Females n = 83,216 (each group)			
Composite outcome, n (%)	28,515 (34.3)	20,770 (25.0)	1.47 (1.44-1.50)
All-cause death, n (%)	10,815 (13.0)	4,336 (5.2)	2.64 (2.54-2.73)
Heart failure, n (%)	10,938 (13.1)	8,605 (10.3)	1.33 (1.29-1.37)
Atrial fibrillation, n (%)	12,644 (15.2)	11,807 (14.2)	1.11 (1.09-1.14)
Severe ventricular arrhythmias, n (%)	1,107 (1.3)	762 (0.9)	1.51 (1.38-1.66)
Myocardial infarction, n (%)	3,757 (4.5)	2,431 (2.9)	1.60 (1.52-1.69)
Takotsubo, n (%)	224 (0.3)	141 (0.2)	1.64 (1.33-2.03)
Patients with multimorbidity n = 56,960 (each group)			
Composite outcome, n (%)	20,038 (35.2)	13,467 (23.6)	1.47 (1.44-1.50)
All-cause death, n (%)	8,845 (15.5)	3,689 (6.5)	2.64 (2.54-2.73)
Heart failure, n (%)	7,092 (12.5)	4,921 (8.6)	1.33 (1.29-1.37)
Atrial fibrillation, n (%)	7,635 (13.4)	6,781 (11.9)	1.11 (1.09-1.14)
Severe ventricular arrhythmias, n (%)	955 (1.7)	663 (1.2)	1.51 (1.38-1.66)
Myocardial infarction, n (%)	3,282 (5.8)	2,043 (3.6)	1.60 (1.52-1.69)
Takotsubo, n (%)	108 (0.2)	88 (0.2)	1.64 (1.33-2.03)
Mild reduced albumin n = 135,572 (each group)			
Composite outcome, n (%)	47,124 (34.8)	36,501 (26.9)	1.37 (1.35-1.39)
All-cause death, n (%)	15,429 (11.4)	6,994 (5.2)	2.31 (2.25-2.38)
Heart failure, n (%)	19,702 (14.5)	16,049 (11.8)	1.28 (1.25-1.31)
Atrial fibrillation, n (%)	22,254 (16.4)	20,716 (15.3)	1.11 (1.09-1.13)
Severe ventricular arrhythmias, n (%)	2,613 (1.9)	1,959 (1.4)	1.38 (1.30-1.57)
Myocardial infarction, n (%)	6,784 (5.0)	4,635 (3.4)	1.51 (1.46-1.57)
Takotsubo, n (%)	239 (0.2)	159 (0.1)	1.54 (1.26-1.89)
Severe reduced albumin n = 56,437 (each group)			
Composite outcome, n (%)	26,914 (45.3)	17,769 (29.9)	1.70 (1.67-1.73)
All-cause death, n (%)	12,881 (21.7)	3,457 (5.8)	4.17 (4.01-4.32)
Heart failure, n (%)	10,060 (16.9)	8,407 (14.1)	1.29 (1.25-1.32)
Atrial fibrillation, n (%)	10,499 (17.7)	9,972 (16.8)	1.12 (1.09-1.15)
Severe ventricular arrhythmias, n (%)	1,443 (2.4)	1,006 (1.7)	1.54 (1.42-1.66)
Myocardial infarction, n (%)	3,839 (6.5)	2,321 (3.9)	1.76 (1.68-1.86)
Takotsubo, n (%)	153 (0.3)	83 (0.1)	1.97 (1.51-2.57)

HR: Hazard Ratio, CI: Confidence of Interval