

RESEARCH ARTICLE

Triglyceride-Glucose Index and Risk of Delirium in Frail Older ICU Patients: A Prospective Observational Study

Kırılğan Yaşlı YBÜ Hastalarında Trigliserit-Glikoz İndeksi ve Deliryum Riski: Prospektif Gözlemsel Bir Çalışma

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ABSTRACT

Objective: Delirium is a frequent and serious neurocognitive complication among older and frail patients in intensive care units (ICUs). The prediction of delirium is crucial for early intervention. The triglyceride-glucose index (TGI), a surrogate marker of insulin resistance, has been associated with metabolic and vascular dysfunction, but its relationship with delirium remains unclear. We aimed to investigate the association between TGI and the development of delirium in frail and older ICU patients.

Material and Method: This prospective, double-blind observational study included frail patients aged ≥ 65 years admitted to tertiary ICUs between April 2024 and March 2025. Frailty was defined as a Rockwood Clinical Frailty Score ≥ 5 . Delirium was diagnosed using the CAM-ICU scale. Fasting triglyceride and glucose levels measured within 24 hours of ICU admission were used to calculate TGI. Categorical variables were compared using Chi-square tests, while continuous variables were analysed using Student's t-test or Mann-Whitney U-test, depending on distribution. ROC curve analysis was performed to assess the predictive value of TGI and other parameters. Multivariate logistic regression was used to identify independent predictors of delirium. A p-value < 0.05 was considered statistically significant.

Results: Of 206 included patients (mean age 72.1 ± 4.6 years), 35.4% developed delirium, predominantly of the hyperactive subtype (84.9%). TGI values were significantly higher in patients with delirium ($p < 0.001$). ROC analysis demonstrated a strong predictive ability for TGI (cut-off > 4.85 , AUC=0.909, sensitivity 86.3%, specificity 87.2%). Multivariate logistic regression identified high TGI, elevated BMI, and male sex as independent predictors of delirium. TGI was not correlated with APACHE II or SOFA scores. Sedation and physical restraint were significantly more frequent in delirious patients.

Conclusion: TGI is a strong and independent predictor of delirium in frail and older ICU patients. Its ease of calculation from routine laboratory values makes it a promising biomarker for the early identification and targeted prevention of delirium in high-risk populations.

Keywords: Delirium; Frailty; Triglyceride-Glucose Index (TGI); Insulin Resistance; Older Patients.

ÖZET

Amaç: Deliryum, yoğun bakım ünitelerindeki (YBÜ) yaşlı hastalar, özellikle de kırılğanlığı olanlar arasında ciddi bir nörokognitif komplikasyondur. Deliryumu öngörmek için erişilebilir ve güvenilir biyobelirteçlerin tanımlanması erken müdahaleyi kolaylaştırabilir ve sonuçları iyileştirebilir. İnsülin direncinin vekil bir belirteci olan trigliserit-glikoz indeksi (TGI), nöroinflamatuvar ve bilişsel süreçlerle ilişkilendirilmiştir. Bu çalışmada, trigliserit-glikoz indeksi ile kırılğan yaşlı YBÜ hastalarında deliryum gelişimi arasındaki ilişkiyi araştırmayı amaçladık.

Gereç ve Yöntem: Bu prospektif gözlemsel çalışmaya üçüncü basamak bir YBÜ'ye kabul edilen 65 yaş ve üzeri 206 kırılğan hasta dahil edilmiştir. Hastalar deliryum açısından YBÜ için Konfüzyon Değerlendirme Yöntemi (CAM-ICU) kullanılarak günlük olarak değerlendirilmiştir. TGI, YBÜ'ye kabul sırasındaki açlık trigliserit ve glukoz düzeylerinden hesaplanmıştır. TGI'nın öngörücü değerini değerlendirmek için çok değişkenli lojistik regresyon ve ROC analizi yapılmıştır. Eğilim skorları bir lojistik regresyon modeli kullanılarak oluşturulmuştur.

Bulgular: Hastaların 73'ünde (%35,4) deliryum gelişmiştir. Orta TGI düzeyi deliryum grubunda deliryum olmayan-

lara kıyasla anlamlı derecede yüksek bulunmuştur (4.97'ye karşı 4.56, $p < 0.001$). Çok değişkenli analizde, TGI bağımsız olarak deliryum ile ilişkili görülmüştür (OR: 2.98, %95 CI: 1.78-5.01, $p < 0.001$). ROC analizi, >4.85 TGI kesme değerinin %86.3 duyarlılık ve %87.2 özgüllük ile 0.909 AUC verdiğini ortaya koymuştur.

Sonuç: TGI, kırılğan yaşlı YBÜ hastalarında deliryum gelişimi ile bağımsız olarak ilişkilidir. Basit ve objektif bir biyobelirteç olarak TGI, YBÜ'lerde erken deliryum risk tabakalandırması için değerli bir araç olarak hizmet edebilir.

Anahtar Sözcükler: Deliryum; Kırılğanlık; Trigliserit-Glikoz İndeksi (TGI); İnsülin 30 Direnci; Yaşlı Hastalar.

As the older adult population increases worldwide, the number of older patients admitted to intensive care is also growing. With the increasing proportion of older patients in intensive care, frailty has become an essential clinical condition (1-4). Frailty is characterised by an increased sensitivity to stress factors due to a decrease in physiological functions (3-7). The prevalence of frailty is 10% in people older than 65 years, and it increases to 26% in people over 75 years (8).

In older patients admitted to the intensive care unit, delirium has an acute onset and fluctuating course. It is characterised by alteration in consciousness, inattention, and cognitive impairment (9, 10). Its prevalence ranges from 45% to 87% in intensive care unit patients (10). Despite this high prevalence, it is difficult to recognise and manage. The underlying pathophysiology is complex, and many causes have been blamed. Critical illnesses, polypharmacy, nerve conduction damage, neuroinflammation, impaired neurotransmitter balance, and metabolic disorders are just a few examples. Just hospitalisation itself can cause delirium.

The presence of delirium is known to contribute to poorer prognoses, such as higher mortality rates, longer durations of mechanical ventilation, and extended ICU and hospitalizations (11). In addition, accumulating evidence suggests that frailty is a major predisposing factor for delirium (12, 13). Numerous biomolecules have been studied in the prediction of delirium. However, the effect of these molecules on prognosis is not yet clear. Cognitive impairment occurs for various metabolic reasons. One of them is insulin resistance (IR). It is characterised by unresponsiveness of target tissues to insulin and impairment in lipid and glucose metabolism (14). Insulin resistance, a core mechanism in metabolic syndrome, has been linked to endothelial dysfunction and cognitive impairment. The Triglyceride-Glucose Index (TGI), as a reliable surrogate marker of insulin resistance as it was evaluated in recent studies (15). It was reported to be a predictor of coronary artery disease, chronic kidney disease, stroke and atherosclerosis (16). The TGI, as a marker of insulin resistance, thus indirectly reflects a state of heightened vulnerability to neurocognitive complications in frail patients. The disruption of the vascular endothelium by IR has caused the need to investigate the effect of this parameter on cognitive impairment. However, very few studies indicate the relationship between the TGI and delirium in intensive care units (17).

Frailty, delirium, and insulin resistance may share overlapping pathophysiological mechanisms. Thus, current study aimed to investigate the development of delirium in frail older ICU patients and to assess the potential predictive role of the triglyceride-glucose

index (TGI) as a surrogate marker of insulin resistance in this patient group.

MATERIAL AND METHOD

Study Design, Approval, and Patients

This was a prospective, single-blind, observational cohort study conducted in a tertiary ICU. Patients were enrolled between April 2024 and March 2025 after ethics committee approval (Fırat University Non-Interventional Research Ethics Committee, No: 23375). Informed consent was obtained from all participants or their legal representatives. Delirium assessments were performed using the CAM-ICU scale by trained ICU physicians who were blinded to patients' laboratory parameters and clinical data at admission. No intervention was applied; patients received standard ICU care. Frailty status was determined at ICU admission using the Rockwood Clinical Frailty Scale. It was registered at 17 May 2024 with the Thai Clinical Trials Registry (ID: TCTR20240517001). The research protocol followed ethical standards the Declaration of Helsinki, and was reported in line with the STROBE recommendations for observational studies.

Patients admitted to the intensive care unit for any reason aged 65 years and older, with RASS ≥ -3 , Rockwood's Clinical Frailty Score (RCFS) ≥ 5 , and speaking Turkish were included in the study. Patients in intensive care for less than 24 hours (death or discharge), All conditions with brain injury (such as traumatic brain injury, ischaemic stroke, haemorrhagic stroke, hypoxic brain injury, hepatic encephalopathy, central nervous system infections), with mental impairment, severe aphasia, coma status or RASS < -3 , patients with dementia or Alzheimer's disease, with hearing loss, with visual loss, with missing data and patients or their relatives not accepting to participate in the study were excluded.

Data Collection

Admission reasons, age, gender, educational status, marital status, body mass index (BMI), smoking, alcohol, and substance abuse history of patients were recorded. According to the referenced criteria, individuals are considered to have severe hearing loss if they cannot follow a conversation at a distance of under one meter, and severe visual loss if they fail to identify two fingers held at that distance (18). The comorbidities of the patients were assessed using the Charlson Comorbidity Index. Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA) scores, mechanical ventilation, renal replacement therapy, sedation or analgesia usage, physical restriction, and the presence of a central catheter

ter and urinary catheter were recorded. The daily physical activities (Activity of Daily Living - ADL) of the patients before coming to the intensive care unit were calculated using the Barthel Index (0-20 fully dependent, 21-61 highly dependent, 62-90 moderately dependent, 91-99 slightly dependent, 100 independent) and then recorded.

In our tertiary intensive care units, laboratory parameters such as biochemistry, blood gas, haemogram, coagulation, acute phase reactants are tested routinely. Fasting glucose and triglyceride levels were recorded once, at ICU admission, and used to calculate the TGI. Triglyceride-glucose index (TGI): Ln was calculated as $[\text{Fasting triglyceride (mg/dl)} \times \text{Fasting glucose (mg/dl)}] / 2$. The routine intensive care management of the patients was not intervened.

Determination of Fragility

The frailty status of the patients was recorded on admission using the Turkish version of Rockwood's Clinical Frailty Score (RCFS) with information obtained from the patients' relatives. The Rockwood's Clinical Frailty Score is scored on a scale of 1-9 depending on the patient's physical reserve. 1: Extremely fit, 9: Terminal stage patient. In our study, patients with RCFS values of 5 and above were considered frail, in accordance with the literature (19).

Detection of Delirium

Since deep sedation or a comatose state should not be present when evaluating patients for delirium, the Richmond Agitation Sedation Scale (RASS; -5 cannot be awakened \rightarrow +4 exhibits aggressive behaviors) was used, and patients with $\text{RASS} \geq -3$ were considered with regard to delirium development. Delirium was assessed using the Confusion Assessment Method-Intensive Care Units (CAM-ICU) (1-Acute change or fluctuations in mental status, 2-Attention deficit/distractibility, 3-Change in level of consciousness, 4-Disordered thoughts). Delirium is diagnosed when criteria 3 or 4 are present alongside criteria 1 and 2. Patients were defined as delirium-positive if the first episode of delirium was detected during their intensive care unit stay. Delirium was considered negative if it did not develop before discharge or death.

Subtypes of delirium were diagnosed using the RASS score. If RASS was between -3 and -1, it was defined as hypoactive delirium; if RASS was between +1 and +4, it was defined as hyperactive delirium (20). We used the Turkish version of CAM-ICU in the assessment. The reliability and applicability of this version was validated in a previous study (21). The physicians who worked shifts in the intensive care units received comprehensive training on delirium assessment and administered the CAM-ICU test twice a day at the same times in the morning and evening. If delirium was suspected, CAM-ICU was applied at that time.

The practitioners had no information about the demographic data and laboratory parameters of the patients. Therefore, our study is a double-blind observational study. The development of delirium was monitored

with the CAM-ICU test until the development of delirium was observed or, if not, to the last day of ICU.

Endpoints

In this study, the primary endpoint was the development of delirium in frail older patients. The secondary endpoints were the relationship between TGI level and delirium development, the rate of delirium development in intensive care, the relationship between delirium, its subtypes and mortality.

Statistical analysis

To determine the number of patients who should be included in the study in line with the main purpose of our research, sample size analysis was performed using the G*power (Version 3.1) package programme before the study. In this direction, the literature was utilised. As a result of the sample size analysis, it was found that a total of 188 patients would be sufficient for sampling for 80% power ($1-\beta=0.80$) and $\alpha=0.05$ error value (95% confidence interval).

The results were analysed using SPSS (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL) 22 software package. Descriptive data were presented as n, % values for categorical data and mean \pm standard deviation (mean \pm standard deviation) values for continuous data. Chi-square analysis (Pearson Chi-square) was used to compare categorical variables between groups. The suitability of continuous variables for normal distribution was analysed by the Kolmogorov-Smirnov test. In the comparison of paired groups, Student t-test was used for normally distributed variables and Mann Whitney U-test was used for non-normally distributed variables. In the comparison of more than two groups, One Way ANOVA analysis was used for variables with normal distribution, and Kruskal Wallis analysis was used for variables without normal distribution.

Receiver operating characteristic (ROC) curve was drawn to measure the contribution of TGI to the development of delirium. Logistic regression analysis was performed to calculate the risk of delirium and mortality. The significant results in pairwise comparison were included in the multivariate model and the Enter method was used. A 1:1 nearest-neighbor propensity score matching (PSM) analysis was performed to reduce confounding effects and balance covariates between delirium and non-delirium groups. The propensity scores were calculated using a logistic regression model including the following variables: age, sex, APACHE II, SOFA, RCFS, ADL, Charlson Comorbidity Index, body mass index (BMI), presence of sepsis, sedation use, and physical restraint. Based on the availability of eligible patients, 73 individuals with delirium were successfully matched with 73 individuals without delirium, resulting in a matched cohort of 146 patients. Matching was performed without replacement, using the nearest neighbor method without applying a caliper. The statistical significance level was accepted as $p < 0.05$ in the analyses.

RESULTS

General Data

During the study period, a total of 463 patients over 65 years of age were admitted to our intensive care units. We excluded 257 of them because they did not fulfill the inclusion criteria (Figure 1).

A total of 206 patients, 95 (46.1%) females and 111 (53.9%) males, were included in the study with a mean age of 72.1±4.6 years. Thirty-five percent of the patients were primary school graduates, 42.7% were high school graduates, and 22.3% were university graduates. Of the 52.4% of the patients were smokers, and 18% were alcohol users. Delirium was observed in 35.4% of patients, of which 57.5% were hyperactive, 15.1% hypoactive and 27.4% mixed type. A total of 64.1% of the patients died. Additional patient characteristics are presented in table 1.

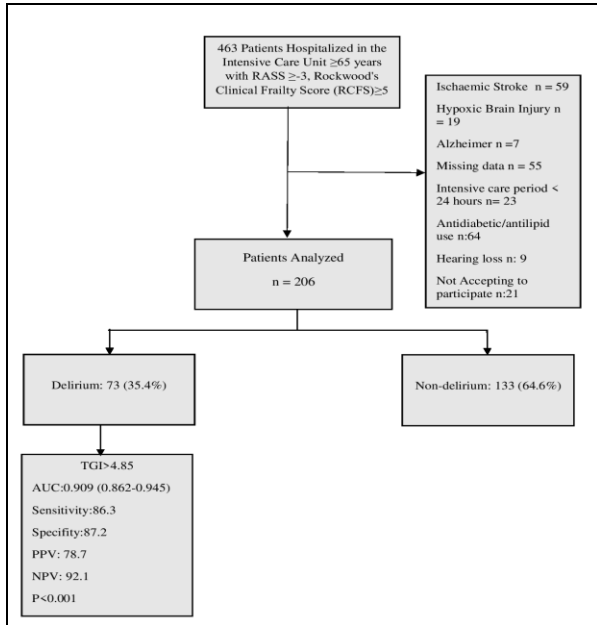


Figure 1. Flow diagram of patient selection and analyse.

Table 1. All characteristics of patients.

		Number	%
Gender	Female	95	46.1
	Male	111	53.9
Age (Years) Median (IQR)		72.0 (68.0-76.0)	
Education	Primary School	72	35.0
	High School	88	42.7
	University	46	22.3
Marital status	Single	43	20.9
	Married	163	79.1
BMI (kg/m²) Med±SD		25.6±4.2	
Cigarette	Yes	108	52.4
	No	98	47.6
Alcohol/Drug Abuse	Yes	37	18.0
	No	169	82.0
CCI, Median (IQR)		4.0 (3.0-6.0)	
RASS, Median (IQR)		0.0 (1.0-1.0)	
ADL, Median (IQR)		65.0 (55.0-75.0)	
RCFS, Median (IQR)		6.0 (5.0-7.0)	
Delirium	Yes	73	35.4
	No	133	64.6
Delirium Type	Hyperactive	42	57.5
	Mixed	20	27.4
	Hypoactive	11	15.1
Duration of delirium development (Days) Median (IQR)		3.0 (3.0-4.0)	
APACHE II, Median (IQR)		22.0 (16.0-30.0)	
SOFA, Median (IQR)		9.0 (5.0-13.0)	
Ventilation requirement	Yes	99	48.1
	No	107	51.9
Renal replacement therapy requirement	Yes	60	29.1
	No	146	70.9
Sedation	Yes	76	36.9
	No	130	63.1
Restriction	Yes	90	43.7
	No	116	56.3
Sepsis	Yes	94	45.6
	No	112	54.4
Central venous catheter	Yes	136	66.0
	No	70	34.0
Glucose, Median (IQR)		102.0 (88.25–113.5)	
Triglycerid, Median (IQR)		153.0 (126.0-195.0)	
TGI, Med±SD		4.8±2	
Mortality	Yes	132	64.1
	No	74	35.9
Length of ICU stay (days) Median (IQR)		9.0 (6.0-14.0)	

Med: Median; SD: Standart Deviation, BMI: Body Mass Index, CCI: Charlson Comorbidity Index, RASS: Richmond Agitation-Sedation Scale, ADL: Activities of Daily Living, RCFS: Rockwood Clinical Frailty Scale, APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Organ Failure Assessment, mTGI: Triglyceride-Glucose Index, ICU: Intensive Care Unit.

Clinical and Biochemical Parameters for Delirium

Body mass index (p =0.004), RASS (p <0.001), CCI (p =0.008), glucose (p =0.001), triglyceride (p =0.001), and TGI (p <0.001) values of patients with delirium were significantly higher than those without delirium. The rate of sedation in patients with delirium (68.5%)

was significantly higher than the rate of sedation in patients without delirium (19.5%) (p <0.001). The rate of restriction in patients with delirium (68.5%) was significantly higher than the rate in patients without delirium (30.1%) (p <0.001) (Table 2).

Table 2. Comparison of the presence of delirium for all parameters.

		Delirium		Non-delirium		p*
		n	% ^a	n	%	
Gender	Female	32	33.7	63	66.3	0.627
	Male	41	36.9	70	63.1	
Age (Years), Median (IQR)		71.0 (68.0-75.0)		72.0 (68.0-76.0)		0.309**
Education	Primary School	51	70.8	21	29.2	0.367
	High School	35	39.8	53	60.2	
	University	17	37.0	29	63.0	
Marital status	Single	13	30.2	30	69.8	0.423
	Married	60	36.8	103	63.2	
BMI (kg/m²) Med±SD		26.7±4.0		24.9±4.2		0.004***
Cigarette	Yes	39	36.1	69	63.9	0.832
	No	34	34.7	64	65.3	
Alcohol/Drug Abuse	Yes	12	32.4	25	67.6	0.673
	No	61	36.1	108	63.9	
Cardiovascular	Yes	27	32.1	57	67.9	0.412
	No	46	37.7	76	62.3	
Respiratory	Yes	36	40.0	54	60.0	0.228
	No	37	31.9	79	68.1	
Renal	Yes	28	39.4	43	60.6	0.384
	No	45	33.3	90	66.7	
GIS	Yes	13	22.8	44	77.2	0.019
	No	60	40.3	89	59.7	
Trauma	Yes	17	29.8	40	70.2	0.298
	No	56	37.6	93	62.4	
Other	Yes	22	40.7	32	59.3	0.343
	No	51	33.6	101	66.4	
CCI, Median (IQR)		4.0 (2.0-5.0)		4.0 (3.0-6.0)		0.008**
RASS, Median (IQR)		1.0 (0.0-1.0)		-1.0 (-1.0-0.0)		<0.001**
ADL, Median (IQR)		65.0 (50.0-70.0)		70.0 (65.0-75.0)		0.002**
APACHE II, Median (IQR)		22.0 (16.0-30.0)		23.0 (16.0-30.0)		0.848**
SOFA, Median (IQR)		8.0 (5.0-12.0)		9.0 (6.0-13.0)		0.369**
Ventilation requirement	Yes	37	37.4	62	62.6	0.576
	No	36	33.6	71	66.4	
RRT requirement	Yes	22	36.7	38	63.3	0.813
	No	51	34.9	95	65.1	
Sedation^b	Yes	50	68.5	26	19.5	<0.001
	No	23	31.5	107	80.5	
Restriction^b	Yes	50	68.5	40	30.1	<0.001
	No	23	31.5	93	69.9	
Central venous catheter	Yes	44	32.4	92	67.6	0.197
	No	29	41.4	41	58.6	
Sepsis	Yes	35	37.2	59	62.8	0.621
	No	38	33.9	74	66.1	
Glucose, Median (IQR)		108.0 (101.0-120.0)		95.0 (85.0-105.0)		0.001**
Triglycerid, Median (IQR)		202.0 (187.0-241.0)		138.0 (113.0-156.0)		0.001**
TGI, Med±SD		5.0±.2		4.7±.2		<0.001***
Mortality^b	Yes	43	58.9	89	66.9	0.252
	No	30	41.1	44	33.1	
Length of ICU stay (days) Median (IQR)		9.0 (5.0-13.0)		9.0 (6.0-15.9)		0.334**

Med: Median, SD: Standart Deviation, BMI: Body Mass Index, CCI: Charlson Comorbidity Index, RASS: Richmond Agitation-Sedation Scale, ADL: Activities of Daily Living, RCFS: Rockwood Clinical Frailty Scale, APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Organ Failure Assessment, RRT: Renal Replacement Therapy, TGI: Triglyceride-Glucose Index, ICU: Intensive Care Unit.

ROC and Regression Analyses

The predictive value of the Triglyceride-Glucose Index (TGI) for the presence of delirium was evaluated using ROC analysis, and an optimal cut-off value was identified. At a cut-off value of >4.85, TGI demonstrated a sensitivity of 86.3% and a specificity of 87.2%, with a positive predictive value of 78.7% and a negative pre-

dictive value of 92.1%. The area under the curve (AUC) was 0.909 (95% CI: 0.862-0.945), indicating that TGI is a strong predictor of delirium (Figure 2).

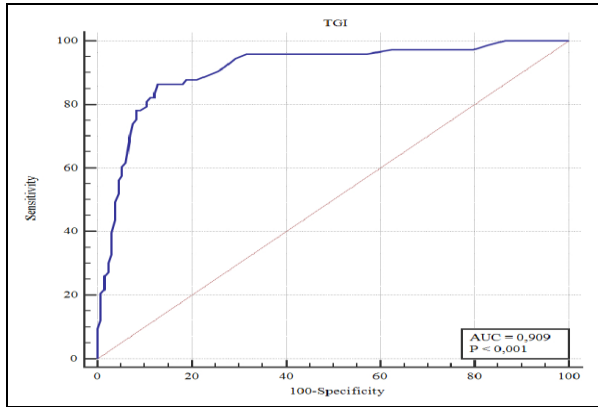


Figure 2. ROC Curve of TGI value for the presence of delirium.

According to the multivariate logistic regression analysis, being male, high BMI, and high TGI were associated with a risk for the presence of delirium (Table 3).

Table 3. Logistic regression analysis of the presence of delirium.

	B	S.E.	p	OR	95% C.I.for EXP(B)	
					Lower	Upper
Age	-.035	.061	0.563	.966	.858	1.087
Male Gender	1.468	.618	0.018	4.341	1.292	14.581
University Graduate			0.883			
Primary School Graduate	.303	.728	0.677	1.354	.325	5.644
High School Graduate	.332	.716	0.643	1.393	.342	5.674
Married	-.032	.674	0.962	.969	.258	3.631
BMI	.140	.059	0.017	1.150	1.025	1.290
CCI	.092	.150	0.537	1.097	.818	1.471
RCFS	-.081	.207	0.696	.922	.615	1.383
ADL	0.020	0.025	0.420	1.020	0.971	1.072
TGI	2.467	0.972	<0.001	3.5139	7.35	16.77
APACHE II	.016	.052	0.759	1.016	.918	1.124
Ventilation Requirement	.479	.564	0.396	1.614	.534	4.875
RRT Requirement	.077	.747	0.918	1.080	.250	4.666
Sedation	1.378	.556	0.013	3.966	1.333	11.802
Restriction	.470	.581	0.419	1.599	.512	4.995
Central Venous Cathater	.613	.810	0.449	1.846	.377	9.030

BMI: Body Mass Index, CCI: Charlson Comorbidity Index, TGI: Triglyceride-Glucose Index, APACHE II: Acute Physiology and Chronic Health Evaluation II, RRT: Renal Replacement Therapy, OR: Odds Ratio; CI: Confidence Interval, SE: Standart Error.

Following propensity score matching based on age, sex, APACHE II, SOFA, RCFS, ADL, CCI, BMI, presence of sepsis, use of sedation, and physical restraints, 73 patients with delirium were matched to 73 patients without delirium. In the matched cohort, the median TGI value was significantly higher in the delirium group compared to the non-delirium group (5.02 (IQR: 4.94-5.13) vs. 4.74 (IQR: 4.52-4.92), respectively; $p < 0.0001$, Mann-Whitney U tes) (Figure 3, Table 4).

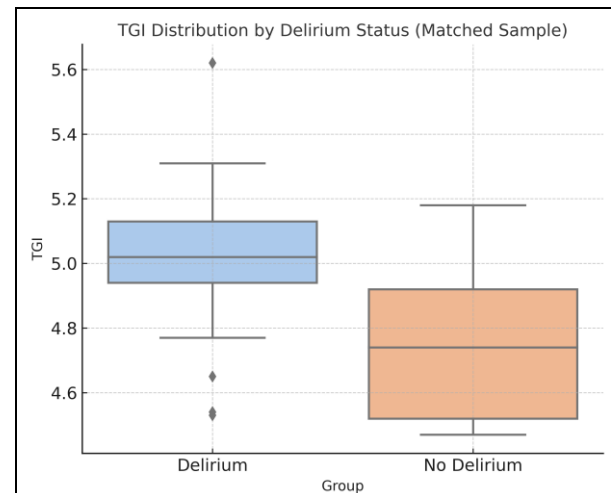


Figure 3. TGI Distribution by Delirium Status.

Table 4. TGI Comparison After Propensity Score Matching.

Group	Median TGI	IQR	Sample size
Delirium	5.02	4.94-5.13	73
No Delirium	4.74	4.52-4.92	73

TGI: triglyceride Glucose Index.

These findings indicate that even after balancing for key clinical confounders, elevated TGI remains significantly associated with delirium development in frail ICU patients.

Clinical and Biochemical Parameters for Mortality

The age ($p = 0.012$), CCI ($p < 0.001$), APACHE2 ($p < 0.001$), and SOFA ($p < 0.001$) values of the de-

ceased were significantly higher than those of the survivors, while the ADL ($p = 0.002$) values were significantly lower. The mortality rate of patients hospitalized in the ICU for renal reasons (73.2%) was significantly higher than that of others (59.3%) ($p = 0.047$). The mortality rate among ventilated patients (78.8%) was significantly higher than that of non-ventilated patients (50.5%) ($p < 0.001$). Additionally, the mortality rate of patients requiring renal replacement therapy (76.7%) was significantly higher than that of those who did not need it (58.9%) ($p = 0.016$). The mortality rate of those with sepsis (78.7%) was significantly higher than that of those without sepsis (51.8%) ($p < 0.001$) (Table 5).

Table 5. Presence of mortality according to all parameters.

		Died		Survived		p*
		n	%	n	%	
Gender	Female	58	61.1	37	38.9	0.402
	Male	74	66.7	37	33.3	
Age (Years), Median (IQR)		73.0 (68.5-77.0)		71.0 (67.0-74.0)		0.012**
Education	Primary School	45	62.5	27	37.5	0.522
	High School	60	68.2	28	31.8	
	University	27	58.7	19	41.3	
Marrital Status	Single	26	60.5	17	39.5	0.579
	Married	106	65.0	57	35.0	
BMI (kg/m²) Med±SD		25.6±4.4		25.5±3.9		0.794***
Cigarette	Yes	66	61.1	42	38.9	0.352
	No	66	67.3	32	32.7	
Alcohol/Drug Abuse	Yes	24	64.9	13	35.1	0.912
	No	108	63.9	61	36.1	
Cardiovascular	Yes	53	63.1	31	36.9	0.807
	No	79	64.8	43	35.2	
Respiratory	Yes	59	65.6	31	34.4	0.697
	No	73	62.9	43	37.1	
Renal	Yes	52	73.2	19	26.8	0.047
	No	80	59.3	55	40.7	
GIS	Yes	34	59.6	23	40.4	0.413
	No	98	65.8	51	34.2	
Trauma	Yes	37	64.9	20	35.1	0.877
	No	95	63.8	54	36.2	
Other	Yes	35	64.8	19	35.2	0.895
	No	97	63.8	55	36.2	
CCI, Median (IQR)		5.0 (4.0-6.0)		3.0 (2.0-4.0)		<0.001**
RASS, Median (IQR)		0.0 (-1.0-1.0)		0.0 (-1.0-1.0)		0.485**
ADL, Median (IQR)		65.0 (50.0-70.0)		70.0 (60.0-75.0)		0.002**
RCFS, Median (IQR)		6.0 (5.0-7.0)		6.0 (5.0-7.0)		0.647**
APACHE II, Median (IQR)		26.0 (18.5-32.0)		18.0 (13.0-23.0)		<0.001**
SOFA, Median (IQR)		10.5 (7.0-13.0)		6.0 (4.0-9.0)		<0.001**
Delirium	Yes	43	58.9	30	41.1	0.252
	No	89	66.9	44	33.1	
Hyperactivity	Hyperactive	23	54.8	19	45.2	0.702
	Hypoactive	7	63.6	4	36.4	
	Mixed	13	65.0	7	35.0	
Length of ICU stay (days) Median (IQR)		3.0 (3.0-4.0)		4.0 (2.0-5.0)		0.708**
Ventilation requirement	Yes	78	78.8	21	21.2	<0.001
	No	54	50.5	53	49.5	
RRT Requirement	Yes	46	76.7	14	23.3	0.016
	No	86	58.9	60	41.1	
Sepsis	Yes	74	78.7	20	21.3	<0.001
	No	58	51.8	54	48.2	
Sedation	Yes	48	63.2	28	36.8	0.833
	No	84	64.6	46	35.4	
Restriction	Yes	56	62.2	34	37.8	0.625
	No	76	65.5	40	34.5	
Glucose, Median (IQR)		100.6 (90-114)		99.2 (87-112)		0.726**
Triglycerid, Median (IQR)		162.6±47.5		159.3±49.8		0.619**
TGI, Median (IQR)		4.8±.2		4.8±.2		0.894***

*Square analysis, **Mann Whitney U test, ***Student t test was applied. Med: Median, SD: Standart Deviation, BMI: Body Mass Index, CCI: Charlson Comorbidity Index, RASS: Richmond Agitation-Sedation Scale, ADL: Activities of Daily Living, RCFS: Rockwood Clinical Frailty Scale, APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Organ Failure Assessment, GIS: Gastrointestinal System, TGI: Triglyceride-Glucose Index, ICU: Intensive Care Unit, RRT: Renal Replacement Therapy.

In the comparison of delirium subtypes, no statistically significant differences were found between the groups in terms of age (p =0.520), sex (p =0.891), BMI (p =0.584), education level (p =0.880), marital status (p =0.189), ADL score (p =0.970), CCI (p =0.614),

APACHE II score (p =0.902), SOFA score (p =0.734), RCFS (p =0.891), presence of sepsis (p =0.864), ICU length of stay (p =0.705), mortality (p =0.975), sedation (p =0.457), use of mechanical ventilation (p =0.147), presence of central venous catheter

(p =0.298), physical restraint (p =0.293), and blood glucose level (p =0.149). However, a statistically significant difference was found in triglyceride levels between the subtypes (p =0.040), with median (IQR) values of 204.5 (198-242) mg/dL in hyperactive, 187.0 (160-204) mg/dL in hypoactive, and 197.5 (179.5-233.5) mg/dL in mixed delirium. TGI values did not

differ significantly between the groups (p =0.833). RASS scores showed a statistically significant difference between the subtypes (p <0.001), with median (IQR) values of +1.0 (0.0-2.0) in hyperactive, -1.0 (-2.0--1.0) in hypoactive, and +1.0 (1.0-1.0) in mixed type (Table 6).

Table 6. Comparison of all parameters according to delirium type.

		Hyperactive		Hypoactive		Mixed		p*
		n	%	n	%	n	%	
Gender	Female	15	35.7	5	45.5	12	60.0	0.196
	Male	27	64.3	6	54.5	8	40.0	
Age (Years), Median (IQR)		70.0 (67.0-74.0)		74.0 (70.0-77.0)		71.0 (68.5-75.5)		0.457**
Education	Primary School	10	23.8	3	27.3	8	40.0	0.708
	High School	21	50.0	5	45.5	9	45.0	
	University	11	26.2	3	27.3	3	15.0	
Marrital Status	Single	10	23.8	0	.0	3	15.0	0.187
	Married	32	76.2	11	100.0	17	85.0	
BMI, Med±SD		26.2±3.7		27.8±4.7		27.2±4.0		0.412***
Cigarette	Yes	23	54.8	7	63.6	9	45.0	0.588
	No	19	45.2	4	36.4	11	55.0	
Alcohol/Drug Abuse	Yes	5	11.9	4	36.4	3	15.0	0.146
	No	37	88.1	7	63.6	17	85.0	
Cardiovascular	Yes	16	38.1	4	36.4	7	35.0	0.971
	No	26	61.9	7	63.6	13	65.0	
Respiratory	Yes	18	42.9	7	63.6	11	55.0	0.394
	No	24	57.1	4	36.4	9	45.0	
Renal	Yes	16	38.1	5	45.5	7	35.0	0.848
	No	26	61.9	6	54.5	13	65.0	
GIS	Yes	10	23.8	1	9.1	2	10.0	0.384
	No	32	76.2	10	90.9	18	90.0	
Trauma	Yes	10	23.8	1	9.1	6	30.0	0.471
	No	32	76.2	10	90.9	14	70.0	
Other	Yes	14	33.3	3	27.3	5	25.0	0.826
	No	28	66.7	8	72.7	15	75.0	
CCI, Median (IQR)		3.5 (2.0-4.0)		4.0 (3.0-5.0)		4.0 (3.0-4.5)		0.74**
RASS, Median (IQR)		1.0 (0.0-2.0) ^a		-1.0 (-2.0—1.0) ^b		1.0 (1.0-1.0) ^a		<0.001**
ADL, Median (IQR)		70.0 (65.0-75.0)		65.0 (55.0-80.0)		67.5 (52.5-75.0)		0.874**
RCFS, Median (IQR)		5.0 (5.0-6.0)		6.0 (5.0-8.0)		5.0 (5.0-6.5)		0.385**
APACHE2, Median (IQR)		21.5 (17.0-30.0)		22.0 (13.0-32.0)		23.0 (16.0-28.0)		0.902**
SOFA, Median (IQR)		8.5 (5.0-12.0)		7.0 (4.0-12.0)		7.5 (5.5-13.0)		0.850**
Duration of delirium development (days), Median (IQR)		3.0 (3.0-5.0)		3.0 (3.0-4.0)		3.5 (3.0-4.0)		0.742**
Ventilation requirement	Yes	18	42.9	8	72.7	11	55.0	0.190
	No	24	57.1	3	27.3	9	45.0	
RRT requirement	Yes	15	35.7	3	27.3	4	20.0	0.441
	No	27	64.3	8	72.7	16	80.0	
Sedation	Yes	31	73.8	6	54.5	13	65.0	0.437
	No	11	26.2	5	45.5	7	35.0	
Restriction	Yes	32	76.2	6	54.5	12	60.0	0.245
	No	10	23.8	5	45.5	8	40.0	
Central Venous Cathater	Yes	23	54.8	7	63.6	14	70.0	0.503
	No	19	45.2	4	36.4	6	30.0	
Mortality	No	19	45.2	4	36.4	7	35.0	0.702
	Yes	23	54.8	7	63.6	13	65.0	
Sepsis	Yes	18	42.9	7	63.6	10	50.0	0.460
	No	24	57.1	4	36.4	10	50.0	
Glucose, Median (IQR)		105.0 (98.0-114.0)		102.0 (100.0-152.0)		112.5 (104.5-144.0)		0.149**
Triglycerid, Median (IQR)		204.5 (198.0-242.0) ^a		187.0 (160.0-204.0) ^b		197.5 (179.5-233.5) ^{a,b}		0.040**
TGI, Med±SD		5.0±.1		5.0±.2		5.0±.3		0.833***
Length of ICU stay (days), Median (IQR)		9.0 (6.0-12.0)		6.0 (5.0-12.0)		9.0 (6.0-16.0)		0.386**

*Square analysis, **Kruskal Wallis analysis, *** One Way ANOVA was applied. Superscript letters (a, b) indicate results of pairwise comparisons using Dunn's post-hoc test. Different letters in the same row denote statistically significant differences between groups (p <0.05). *Med*: Median, *SD*: Standart Deviation, *BMI*: Body Mass Index, *CCI*: Charlson Comorbidity Index, *RASS*: Richmond Agitation-Sedation Scale, *ADL*: Activities of Daily Living, *RCFS*: Rockwood Clinical Frailty Scale, *APACHE II*: Acute Physiology and Chronic Health Evaluation II, *SOFA*: Sequential Organ Failure Assessment, *GIS*: Gastrointestinal System, *TGI*: Triglyceride-Glucose Index, *ICU*: Intensive Care Unit, *RRT*: Renal Replacement Therapy.

DISCUSSION

In this prospective observational study, we showed that a higher TGI at ICU admission was strongly linked to the development of delirium in frail older adults. Patients who experienced delirium had notably higher TGI levels compared to those without delirium, highlighting a possible connection between metabolic dysregulation and acute brain dysfunction in seriously ill geriatric patients.

The TGI is a validated surrogate marker of insulin resistance and is increasingly recognized as a systemic metabolic risk indicator. Its clinical usefulness has been demonstrated in cardiovascular disease, stroke, and neurocognitive disorders (17). Delirium, a multifactorial syndrome characterized by sudden cognitive impairment, results from a complex interplay of neuroinflammation, oxidative stress, metabolic disturbances, and endothelial dysfunction—all of which are associated with insulin resistance. Therefore, our findings are physiologically plausible and align with existing literature emphasizing insulin resistance and metabolic dysregulation in the development of delirium.

Delirium is a common and serious complication in intensive care, particularly among older and frail individuals. Advanced age and frailty increase vulnerability to delirium due to impaired physiological reserve, reduced cognitive capacity, and heightened inflammatory responses (22-24, 29). In a large prospective study, frailty increased the risk of delirium by 60% and was associated with higher mortality (12). In our study, we included patients with an RCFS score -3 to $+4$, forming a homogeneously frail cohort with a mean age of 72.1 years and a delirium incidence of 35.4%. Additionally, significantly lower ADL scores in delirious patients further support the association between functional dependence and heightened delirium risk. Delirium not only results in temporary or permanent cognitive decline in frail older adults but also delays recovery, impedes return to independent daily living, and increases healthcare costs (25). Therefore, early identification and prevention of delirium are critical priorities in the ICU setting (26).

Previous studies have demonstrated that the incidence of delirium can be reduced by up to 40% through the recognition of modifiable risk factors and the implementation of targeted preventive strategies (27). Multi-component interventions such as the ABCDEF bundle—which includes spontaneous awakening and breathing trials, sedation coordination, regular delirium monitoring, early mobilization, and family engagement—have been shown to decrease delirium rates (28). However, the comprehensive application of such bundles requires significant clinical resources. Therefore, there is a need for simple, accessible, and objective biomarkers to help identify high-risk patients early and support preventive decision-making. Our study addresses this need by exploring the role of the TGI as a potential predictor of

delirium in this vulnerable population. To our knowledge, this is one of the few studies to evaluate the role of TGI in ICU delirium among frail older adults, a population particularly susceptible to both metabolic and cognitive disturbances.

Frailty is characterized by diminished physiological reserve and heightened susceptibility to homeostatic disruption. The combination of frailty and elevated TGI may represent a "metabolic frailty phenotype" that predisposes to acute brain dysfunction under the stress of critical illness. The strong predictive value of TGI in our cohort supports this hypothesis. Since TGI is a practical and indirect measure of insulin resistance, it is strongly correlated with standard methods such as the hyperinsulinaemic euglycaemic clamp test (HEC) and HOMA (30). Insulin resistance has been shown to negatively affect neurological function and may contribute to cognitive impairment through mechanisms involving tau phosphorylation, A β accumulation, and disrupted insulin signaling (31-33). Associations between preoperative IR and postoperative delirium, as well as Alzheimer's disease biomarkers, have also been reported (34). Moreover, IR-related endothelial dysfunction has been linked to cognitive decline via atherosclerosis and dyslipidemia (35). Sun et al. identified TGI as an independent risk factor for postoperative delirium in patients with type 2 DM (36), while Huang et al. showed that elevated TGI predicted both delirium and mortality in elderly ICU patients (17). Consistent with these findings, our study confirmed the independent predictive value of TGI for delirium in frail ICU patients using multivariate regression model. To strengthen the validity of our findings, we performed propensity score matching to balance key confounding variables between the delirium and non-delirium groups. Even after matching, the TGI remained significantly higher in patients with delirium, supporting its potential role as an independent metabolic biomarker associated with acute cognitive dysfunction. This reinforces the hypothesis that systemic metabolic dysregulation, particularly insulin resistance, may contribute to the pathophysiology of delirium in frail ICU populations.

In ROC analysis, we observed that TGI with a cut-off value >4.85 had a high diagnostic accuracy with an area under the curve (AUC) of 0.909, showing a sensitivity of 86.3% and specificity of 87.2%. Our findings align with previous studies that identified metabolic dysregulation as a key contributor to acute cognitive impairment. However, further large-scale prospective studies are warranted to validate the diagnostic thresholds and explore the integration of TGI into comprehensive delirium risk prediction models.

In addition to the strong predictive performance of TGI, our study identified other relevant clinical associations. Body mass index (BMI) was significantly higher in patients with delirium, suggesting that obesity-related systemic inflammation may contribute to cognitive vulnerability (14). Interestingly, well-established ICU severity scores such as APACHE II and SOFA did

not show significant associations with delirium occurrence in this cohort, which further highlights the potential prognostic utility of specific metabolic markers like TGI. Furthermore, delirious patients were significantly more likely to receive sedation and physical restraint compared to non-delirious patients. This observation may reflect both reactive clinical management in response to agitation, and possibly, the iatrogenic role of physical restraint in delirium onset. Although causality cannot be established from this observational data, these findings underscore the importance of cautious sedation practices and minimizing the use of restraints in high-risk patients.

In addition to the primary analysis, we conducted a detailed subgroup analysis based on delirium subtypes—hyperactive, hypoactive, and mixed. In our study cohort, hyperactive delirium was the most common subtype (46.7%), followed by mixed (29.3%) and hypoactive (24.0%) types. Interestingly, this distribution differs from most of the existing literature, where hypoactive delirium is typically reported as the predominant subtype, especially among older ICU patients. The discrepancy may stem from methodological factors such as closer monitoring and structured delirium assessments in our study, which may have led to better detection of agitated behavior associated with hyperactive delirium. Additionally, cultural and clinical differences in sedation practices, restraint use, or ICU staffing may influence delirium subtype prevalence across settings. The predominance of hyperactive delirium in our cohort may partly reflect detection bias, as clinicians more easily recognize agitated behaviors compared to hypoactive presentations. Standardization of assessment training and the use of continuous observation tools may reduce this bias in future research.

While TGI values did not significantly differ between delirium subtypes, serum triglyceride levels were significantly lower in patients with hypoactive delirium compared to those with hyperactive delirium. This finding may reflect divergent metabolic or inflammatory profiles between subtypes. The clinical parameters such as age, sex, BMI, illness severity (APACHE II, SOFA), comorbidity burden, functional status, ICU length of stay, and mortality were comparable across subtypes.

Although TGI was significantly associated with the presence of delirium, we did not observe a statistically significant difference in TGI levels between survivors and non-survivors in our cohort. This finding suggests that TGI may not independently predict mortality among frail ICU patients. One possible explanation is that TGI reflects a metabolic vulnerability, such as insulin resistance and endothelial dysfunction, that primarily contributes to neurocognitive complications like delirium rather than directly influencing survival outcomes. Additionally, mortality in the ICU is a multifactorial endpoint influenced by various acute physiological insults, disease severity, and comorbid conditions. In our study, classical severity scores such as

APACHE II and SOFA were significantly higher in patients who died.

Several strengths of our study should be noted. The prospective design and systematic delirium assessment using the CAM-ICU enhance the internal validity. We focused specifically on a frail elderly population, in whom delirium has both higher prevalence and greater prognostic impact. The use of validated measurement tools such as CAM-ICU, RCFS, and Barthel ADL supports methodological reliability. Confounding factors were controlled using multivariate logistic regression, and robustness was further improved through propensity score matching. Even after matching, TGI remained significantly higher in delirium patients, reinforcing the potential of TGI as an independent biomarker. The calculation of TGI from routine laboratory data provides an additional advantage for its clinical use. Our findings suggest that TGI may be an easily available and reliable parameter for the prediction of neurocognitive complications in intensive care conditions.

On the other hand, the single-center nature of the study and the relatively small sample size which may not fully represent the broader ICU population and may limit its generalizability. Multicenter studies with larger sample sizes are warranted to validate the predictive value of TGI and confirm its external applicability across diverse ICU settings. Another limitation is that the long-term outcomes and costs of delirium were not investigated. However, this did not affect our results because we examined whether TGI is an independent risk factor for the development of delirium. Another important limitation is the lack of control for potential confounding factors affecting glucose levels. In this study, patients with diabetes mellitus, those receiving corticosteroids, or those under glucose infusion were not excluded. These interventions and conditions may have influenced fasting glucose values and, consequently, the TGI. However, we intentionally retained these patients in order to reflect the metabolic and therapeutic complexity of real-life ICU populations. This approach enhances the external validity of our findings but may have introduced some variability in the interpretation of TGI values. In addition, insulin resistance was assessed only by TGI, and direct methods such as the HEC test or HOMA-IR were not used. Another limitation is that the TGI was only measured on ICU admission, and dynamic changes in metabolic status over time were not assessed. Given that glucose and triglyceride levels can be influenced by stress responses, medications (e.g., steroids), and feeding strategies, a single measurement may not fully reflect ongoing metabolic risk. The other limitation is, TGI was measured only once at ICU admission. Serial monitoring throughout the ICU stay could have provided a better understanding of metabolic fluctuations related to delirium risk. The observation of hyperactive delirium as the predominant subtype in our study may be due to the fact that hypoactive delirium could be mistaken for depression, fatigue, or a general state of illness,

making it more difficult to recognize clinically with the CAM-ICU scale we used. The fluctuating course of delirium, especially in mixed-type delirium, leads to the alternation of both hypoactive and hyperactive features of motor symptoms, complicating subtype classification. Glucose-modifying factors such as diabetes mellitus, corticosteroid therapy, and glucose infusions were not excluded, which might have influenced fasting glucose and TGI values. Future studies should consider subgroup analyses adjusting for these confounders.

Conclusion

This study revealed that TGI was significantly associated with the development of delirium and was an independent risk factor in frail older patients admitted to the intensive care unit. The feasibility of TGI suggests that it may be an effective biomarker in the early diagnosis of neurocognitive complications such as delirium. Given its simplicity and reliance on routinely measured laboratory parameters, TGI could serve as a practical bedside biomarker to support early delirium risk stratification in frail elderly ICU patients.

Ethics approval and consent to participate

This study was approved by the Firat University Non-Interventional Research Ethics Committee on 27 March 2024 (approval no: 23375). Written informed consent to participate was obtained from all patients or their legally authorised representatives. The research protocol followed ethical standards the Declaration of Helsinki, and was reported in line with the STROBE recommendations for observational studies.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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