

# Predictive Value of Electrocardiogram for Intracranial Hemorrhage After Thrombolysis in Acute Ischemic Stroke Patients: Retrospective Single-center Cohort Study

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## Abstract

**Aim:** Intravenous thrombolytic therapy (IVT) is an effective treatment modality for acute ischemic stroke (AIS). However, post-treatment intracranial hemorrhage (ICH), particularly symptomatic ICH (sICH), is associated with significant morbidity and mortality. This study aims to investigate the relationship between electrocardiogram (ECG)-detected left ventricular hypertrophy (LVH) and the risk of hemorrhage following IVT.

**Materials and Methods:** Patients who received IVT for AIS between 2022 and 2025 in a tertiary care center were retrospectively analyzed. LVH was assessed using the Gubner, Cornell, and Sokolow-Lyon ECG criteria. The primary endpoint was the development of sICH after IVT. The predictive power of ECG voltage criteria for LVH was evaluated using ROC curve analysis, and both univariable and multivariable logistic regression analyses were conducted.

**Results:** A total of 135 patients were included. The incidence of sICH was 11%. Increased voltage (R I + S III) according to the Gubner criterion and elevated systolic blood pressure were identified as independent risk factors for sICH ( $p < 0.01$ ). The area under the curve values for the Gubner and Cornell criteria in predicting sICH were 0.764 and 0.751, respectively. The Gubner criterion exhibited a sensitivity of 60% and a specificity of 80.8%, whereas the Cornell criterion demonstrated higher sensitivity (66.7%) but comparatively lower specificity (65.0%). The Sokolow-Lyon criterion was not statistically significant ( $p = 0.237$ ).

**Conclusion:** ECG-LVH may serve as a simple adjunct marker to identify patients at higher risk of sICH after IVT, but further validation is required.

**Keywords:** Stroke, intracranial hemorrhage, electrocardiography

## Introduction

Intravenous thrombolytic therapy (IVT) with recombinant tissue plasminogen activator (rtPA) remains the cornerstone of treatment for acute ischemic stroke (AIS), particularly when administered within the therapeutic window. Despite its effectiveness in restoring cerebral perfusion, one of the most feared complications of rtPA is symptomatic intracranial hemorrhage (sICH) (1).

This condition adversely affects post-treatment prognosis and constitutes a major limitation to the broader use of thrombolytic therapy. Numerous studies in the literature have investigated the predictors of post-thrombolytic hemorrhage, with cerebral microbleeds (CMB) being particularly associated with increased risk (2,3). CMB is small, round hemosiderin deposits resulting from chronic small vessel leakage, and they are detectable by magnetic resonance imaging (MRI) (4). However, due to the



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need for urgent decision-making in acute stroke management, imaging is often limited to non-contrast computed tomography (CT), which restricts the evaluation of CMB.

Given the time-sensitive nature of stroke management, it is crucial that emergency physicians, neurologists, and intensive care specialists possess adequate knowledge of thrombolytic therapy and its potential complications (5). Previous studies have highlighted variability in physicians' knowledge regarding thrombolytic treatment and emphasized the importance of continuous training and protocol optimization in acute stroke care (6,7).

Although the association between CMB and increased hemorrhagic risk is well established, the inability to assess these lesions in the emergency department (ED) creates a significant diagnostic gap. Therefore, in situations requiring rapid decision-making under ED conditions, there is a need for easily accessible and applicable alternatives to advanced imaging techniques. Since chronic hypertension is the most common underlying cause of CMB, its indirect assessment through organ-based manifestations gains clinical importance in this context (8). Electrocardiography (ECG) could be a pragmatic, accessible tool, especially where MRI is not feasible. ECG-detected left ventricular hypertrophy (LVH) is the most prominent cardiac manifestation of chronic hypertension and may reflect chronic microvascular involvement. However, the association between this form of electrical remodeling and the development of ICH following IVT has not been adequately investigated in the literature.

In this retrospective cohort study, we aimed to investigate the relationship between ECG findings of LVH and the risk of both sICH and overall ICH in patients receiving IVT for AIS. If an increased risk of sICH is demonstrated among patients with LVH on ECG, this may represent a clinically valuable marker to support patient selection and ensure safer administration of IVT.

## Materials and Methods

### Patients and Study Design

This was a single-center retrospective cohort study conducted in a tertiary ED between 2022 and 2025, including patients diagnosed with AIS who received IVT. The study was approved by the University of Health Sciences Türkiye, Ankara Etlik City Hospital Ethics Committee (decision no: AEŞH-BADEK-2025-0230; date: 26.02.2025). It was conducted in accordance with the Declaration of Helsinki, and all patient data collected by the researchers were kept confidential.

Patients with a pre-stroke Modified Rankin scale (mRS) score greater than 2, patients with Alzheimer's disease, Parkinson's

disease, or other neurodegenerative disorders, and those without available ECG data were excluded, as these conditions may cause cognitive impairment or confounding neurological deficits that could bias functional outcome assessment. In addition, patients with a history of major brain surgery, those on anticoagulant therapy, and those with inadequate brain imaging were excluded based on the predefined criteria.

### Data Collection and Handling of Missing Data

Data were obtained using the hospital's electronic medical record system. Sociodemographic characteristics such as age and sex, vital signs (blood pressure, heart rate, respiratory rate, and oxygen saturation), laboratory parameters (hemoglobin, platelet count, urea, creatinine, and lactate), and patients' current medications were recorded on a standardized data collection form. mRS scores, assessed at the time of hospital admission, were also recorded (9). The etiology of ischemic stroke was classified according to the Trial of Org 10172 in acute stroke treatment criteria (10). The Alberta Stroke Program Early CT Score (ASPECTS) was calculated for the patients included in the study group (11). Additionally, three-month mortality and mRS scores at the end of the third month were obtained from the patients' electronic records.

Missing data were carefully assessed; variables with excessive missingness were excluded from the final analyses. In particular, onset-to-treatment time (OTT) was missing in the majority of patients and therefore was not included in the statistical models.

### Calculation of MARS and Fazekas Scale

The Microbleed Anatomical Rating scale (MARS) was independently applied by a radiologist with 17 years of experience in neuroimaging, who was blinded to the clinical data of the patients (12). The evaluation was conducted in three stages. In the first stage, each microbleed lesion was classified as either "definite" or "possible." "Definite" lesions were defined as round, well-demarcated, hypointense foci ranging in diameter from 2 to 10 mm. "Possible" lesions were those with less distinct borders and uncertain differentiation. For lesions located in the basal ganglia, corresponding regions were carefully examined on T2-weighted and FLAIR sequences to rule out infarcts or calcifications. Vascular structures that could mimic microbleeds, imaging artifacts, air–bone interfaces, non-microbleed small hemorrhages, and mineralization foci were also meticulously evaluated.

In the second stage, microbleeds were anatomically categorized into three regions: deep, lobar, and infratentorial. Deep microbleeds included lesions located in the basal ganglia, thalamus, the internal and external capsules, corpus callosum,

and deep or periventricular white matter. Lobar microbleeds were defined as those localized to cortical or subcortical areas. Infratentorial microbleeds encompassed those identified in the brainstem and cerebellum. In the final stage, the total MARS score was calculated by summing the number of microbleeds observed in the aforementioned regions.

Leukoaraiosis (white matter lesions) was evaluated using the Fazekas scale on FLAIR MRI sequences. The Fazekas score was assigned separately for periventricular and deep white matter hyperintensities, each rated from 0 to 3. Periventricular signal abnormalities were assessed based on the presence of caps, rims, or extensive lesions, while deep white matter lesions were scored according to the number, size, and degree of confluence. The sum of both subscores constituted the total Fazekas score.

### Evaluation of Electrocardiographic and Echocardiographic Left Ventricular Hypertrophy

For the assessment of LVH on ECG, three commonly used criteria were adopted: the Cornell voltage criterion (13), the Gubner criterion (14), and the Sokolow-Lyon criterion (15), each representing unipolar limb, bipolar limb, and chest leads. All ECGs were independently evaluated by three emergency medicine specialists blinded to the hemorrhagic outcomes. For each ECG, the average of the voltage measurements was calculated, and it was subsequently reviewed and confirmed by the cardiologist who was also blinded to clinical outcomes. The values approved by the cardiologist were used for statistical analysis. Although blinding was ensured, inter-rater reliability among the emergency specialists was not measured, which represents a limitation of the ECG interpretation process.

The definitions for the three voltage criteria were as follows:

Cornell voltage criterion: Male:  $RaVL + SV3 > 28 \text{ mm}$  ( $=2.8 \text{ mV}$ ),  
Female:  $RaVL + SV3 > 20 \text{ mm}$  ( $=2.0 \text{ mV}$ )

Gubner voltage criterion:  $RI + SIII \geq 25 \text{ mm}$  ( $=2.5 \text{ mV}$ )

Sokolow-Lyon criterion:  $SV3 + RV5 \text{ or } V6 > 35 \text{ mm}$  ( $=3.5 \text{ mV}$ )

In our hospital, echocardiographic (ECHO) evaluation is routinely performed within one week of hospitalization in patients diagnosed with AIS. ECHO reports and archived imaging were reviewed by a cardiologist experienced in echocardiography. LVH was recorded in the data form if the left ventricular wall thickness exceeded 11 mm in men or 10 mm in women.

### Intracranial Hemorrhage Outcome

Any ICH detected by CT within 24 hours after rtPA administration was defined as post-thrombolytic ICH. In clinical practice, post-

thrombolytic ICH includes both sICH and asymptomatic ICH. Symptomatic hemorrhages were classified according to the Heidelberg Bleeding Classification, which involves a structured seven-step process for categorizing hemorrhagic events (16). In this study, the Heidelberg classification was performed by more than one reviewer; however, inter-rater reliability was not assessed, which represents a limitation of the outcome definition. However, due to the inherent limitations of retrospective data review, hemorrhages were defined in this study as events associated with any of the following:  $\geq 4$ -point worsening in the total National Institutes of Health Stroke scale (NIHSS) score compared to the most recent pre-deterioration assessment (not baseline);  $\geq 2$ -point worsening in any individual NIHSS category (to detect new hemorrhages causing new symptoms); or the need for intubation, hemicraniectomy, external ventricular drainage, or other major medical/surgical interventions.

The anatomical classification of ICH was conducted according to the predefined criteria summarized in Table 1.

### Sample Size

Based on previous studies that reported a 30% incidence of ICH in patients who received thrombolytic therapy for AIS (17), and assuming a clinically meaningful difference in the prevalence of LVH between those with and without ICH (18), it was estimated that a minimum of 24 patients with ICH would be sufficient to achieve 85% statistical power with a two-sided alpha of 0.05. The post-hoc power was computed in G\* Power (Exact test; one-sample proportion, two-tailed,  $\alpha=0.05$ ) using the expected ICH incidence under H0 of 30% and the observed incidence of 17.8% with  $n=135$ . The achieved power was approximately 66%.

**Table 1. Anatomical classification of intracranial hemorrhage according to the Heidelberg bleeding classification**

Class	Type	Description
1		Hemorrhagic transformation of infarcted brain tissue
	HI <sup>1</sup>	Scattered small petechiae, no mass effect
	HI <sup>2</sup>	Confluent petechiae, no mass effect
2	PH <sup>1</sup>	Hematoma within infarcted tissue, occupying $<30\%$ , no substantive mass effect
	PH <sup>2</sup>	Hematoma occupying $\geq 30\%$ of infarcted tissue, with significant mass effect
3		Intracerebral hemorrhage outside infarcted tissue or extracerebral bleeding
	3 <sup>a</sup>	Parenchymal hematoma remote from infarcted tissue
	3 <sup>b</sup>	Intraventricular hemorrhage
	3 <sup>c</sup>	Subarachnoid hemorrhage
	3 <sup>d</sup>	Subdural hemorrhage

### Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as medians and interquartile ranges (IQRs), while categorical variables were expressed as frequencies and percentages. Between-group comparisons were performed using the Mann-Whitney U test for continuous variables and the Chi-square or Fisher’s exact test for categorical variables, as appropriate.

To evaluate the predictive performance of ECG LVH criteria for sICH, ROC curve, analysis was conducted, and area under the curve (AUC), optimal cut off values, sensitivity, and specificity were reported. Univariable and multivariable logistic regression analyses were used to identify independent predictors of sICH. Variables with a p value <0.20 in univariable analysis were included in the multivariable model. A two-sided p value of <0.05 was considered statistically significant.

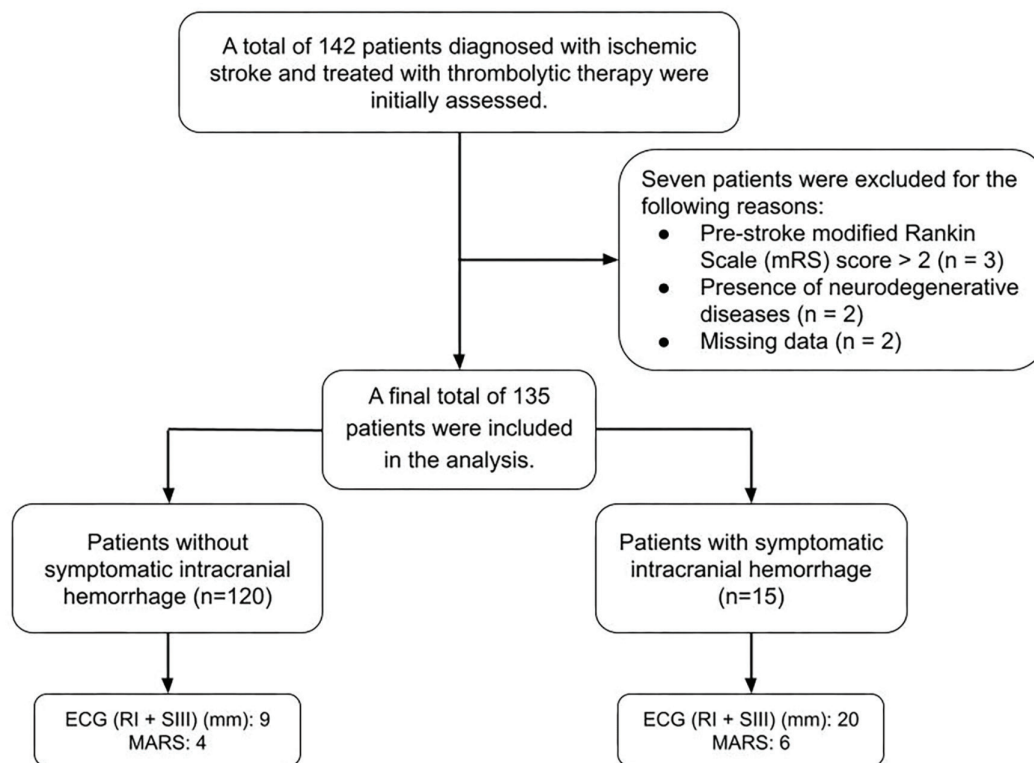
### Results

A total of 135 patients diagnosed with AIS and treated with IVT were included in the final analysis. Figure 1 presents the patient selection process and flowchart. The mean age of the cohort was 67.2±14.8 years, and 60.7% (n=82) were male. The median systolic

and diastolic blood pressures at presentation were 150.5 mmHg and 89 mmHg (IQR: 80-95), respectively. Table 2 summarizes the baseline demographic and clinical characteristics of the study population.

When stratified by the presence of sICH, no significant differences were observed in age or sex. However, systolic and diastolic blood pressures were significantly higher in the sICH group (p=0.002 and p=0.004, respectively). While ASPECTS and MARS scores did not differ significantly between groups, the 3-month mRS score was lower in the sICH group (p=0.005), likely reflecting the significantly higher mortality observed in this group (40% vs. 8%, p<0.001). There was no statistically significant difference in the rate of bridging therapy between patients with and without ICH, and between those with and without sICH. These findings are presented in Table 3. Detailed data are provided in Supplementary Table 1.

For predicting ICH, the Cornell voltage criterion demonstrated the highest [AUC: 0.641, 95% confidence interval (CI): 0.510-0.773, p=0.030], with 83.3% sensitivity and 27% specificity. The Gubner criterion also reached statistical significance (AUC: 0.628, 95% CI: 0.491–0.766, p=0.049), whereas the Sokolow-Lyon criterion did not show a significant discriminative ability (p=0.398) (Figure 2).



**Figure 1.** Flowchart of patient selection and group stratification  
ECG: Electrocardiogram, MARS: Microbleed Anatomical Rating scale

<b>Table 2. General characteristics of the study population</b>	
<b>Variables (n=135)</b>	
<b>Sex</b>	
Female	53 (39.3%)
Male	82 (60.7%)
Age	67.19±14.78
<b>Vital parameters</b>	
Systolic blood pressure (mmHg)	150.5±21.96
Diastolic blood pressure (mmHg)	89 (IQR: 80-95)
Pulse (beat/minute)	76 (IQR: 69-87)
Respiratory rate (per minute)	20 (IQR: 18-20)
Oxygen saturation (%)	95 (IQR: 92-97)
<b>Pharmacological therapies administered</b>	
Antiplatelet therapy	59 (43.7%)
Anticoagulant therapy	10 (7.4%)
Statin therapy	15 (11.1%)
Antihypertensive therapy	84 (62.2%)
<b>Laboratory parameters</b>	
Hemoglobin (g/dL)	13.9±2.09
Platelet count (.103/L)	242.8±75.8
Urea level (mg/dL)	36.9 (IQR: 28-48.5)
Creatinine level (mg/ dL)	0.9 (IQR: 0.78-1.09)
Lactate level (mmol/L)	1.81 (IQR: 1.38-2.28)
<b>Trial of Org 10172 for acute stroke treatment classification</b>	
Large-artery atherosclerosis	85 (63%)
Cardioembolic stroke	23 (17%)
Small-vessel disease/penetrating artery disease	12 (8.9%)
Stroke of other determined cause	8 (5.9%)
Stroke of undetermined cause (cryptogenic stroke)	7 (5.2%)
<b>Alberta stroke program early CT score</b>	9 (IQR: 7-10)
<b>Microbleed Anatomical Rating scale</b>	4 (IQR: 2-6)
<b>Fazekas scale score (n=87)</b>	
Periventricular white matter	2 (IQR: 1-2)
0 =no lesion	11 (12.6%)
1 =“caps” or pencil-thin lining	32 (36.8%)
2 =smooth “halo”	41 (47.1%)
3 =irregular periventricular signal extending into the deep white matter	3 (3.4%)
<b>Deep white matter</b>	1 (IQR: 1-2)
0 =no lesion	16 (18.4%)
1 =punctate lesions	37 (42.5%)
2 =beginning confluence	31 (35.6%)
3 =extensive confluent areas	3 (3.4%)
<b>Modified Rankin scale at administration</b>	3 (IQR: 3-4)
<b>Post- thrombolytic bleeding</b>	
Yes	24 (17.8%)
<b>Heidelberg bleeding classification (n=24)</b>	
Class 1: hemorrhagic transformation of infarcted brain tissue	1
1 <sup>a</sup> : HI1: scattered small petechiae, no mass effect	2
1 <sup>b</sup> : HI2: confluent petechiae, no mass effect	6
1 <sup>c</sup> : PH1: hematoma within infarcted tissue, occupying <30%, no substantive mass effect	
Class 2: intracerebral hemorrhage within and beyond infarcted brain tissue	4
PH <sup>2</sup> : hematoma occupying ≥30% of the infarcted tissue, with obvious mass effect (PH <sup>2</sup> )	
Class 3: intracerebral hemorrhage outside the infarcted brain tissue or intracranial-extracerebral hemorrhage	
3 <sup>a</sup> : parenchymal hematoma remote from infarcted brain tissue	1
3 <sup>b</sup> : intraventricular hemorrhage	2
3 <sup>c</sup> : subarachnoid hemorrhage	7
3 <sup>d</sup> : subdural hemorrhage	1

<b>Table 2. Continued</b>	
<b>Variables (n=135)</b>	
<b>Electrocardiographic criteria of left ventricular hypertrophy</b>	
The Gubner criteria (voltage) Hypertrophic (R I + S III >25 mm)	9 (IQR: 6-15) mm 11 (8.1%)
<b>The Sokolow-Lyon criteria (voltage)</b> Hypertrophic (S V3 + R V5-6 >35 mm)	16.5 (IQR: 12-22) mm 5 (3.7 %)
The Cornell Voltage Criteria (voltage) Hypertrophic (R aVL + S V3 >35 mm for men, >25 mm for women)	14 (IQR: 9-18) mm 6 (4.4%)
Hypertrophic findings at echocardiography (*n=115)	38 (33%)
Length of hospital stay (days)	8 (IQR: 5-13)
Modified Rankin scale at 3 <sup>rd</sup> month	3 (IQR: 1-3)
Bridging therapy (mechanical thrombectomy)	32 (24 %)
Symptomatic intracranial hemorrhage	15 (11 %)
<b>Survey</b>	
Alive	119 (88.1%)
Died	16 (11.9%)
*Number of patients that performed echocardiography. All data are presented as counts and percentages for categorical variables, and as either mean ± standard deviation or median and interquartile range (IQR: 25 <sup>th</sup> -75 <sup>th</sup> percentiles), depending on the distribution of the data, and adherence to normality assumptions CT: Computed tomography, IQR: Interquartile range	

<b>Table 3. Comparison of clinical, radiological, and electrocardiographic characteristics according to the presence of intracranial hemorrhage and symptomatic intracranial hemorrhage</b>			
<b>Variables</b>	<b>Yes (n=24)</b>	<b>No (n=111)</b>	<b>p value</b>
<b>Outcome 1: intracranial hemorrhage</b>			
<b>Sex</b>			
Female	12 (50%)	41 (36.9%)	0.235
Male	12 (50%)	70 (63.1%)	
<b>Age</b>	72.08±11.86	66.13±15.17	0.073
<b>Vital parameters</b>			
Systolic blood pressure (mmHg)	164.5 (IQR: 142.5-177.5)	145 (IQR: 135-159)	<b>0.004</b>
Diastolic blood pressure (mmHg)	92.5 (IQR: 87-100)	88 (IQR: 80-93)	0.066
<b>Microbleed Anatomical Rating scale</b>	5 (IQR: 3-6.75)	4 (IQR: 2-6)	0.205
<b>Survey</b>			
Died	10 (42%)	6 (5%)	<b>&lt;0.001</b>
<b>Electrocardiographic criteria of left ventricular hypertrophy</b>			
The Gubner criteria (voltage) Hypertrophic (R I + S III >25 mm)	9 (IQR: 6-13) mm 6 (25%)	6 (IQR: 12-26) mm 5 (4.5%)	0.083 <b>&lt;0.001</b>
The Sokolow-Lyon criteria (voltage) Hypertrophic (S V3 + R V5-6 >35 mm)	16 (IQR: 13-23) mm 2 (8.3%)	17 (IQR: 12-22) mm 3 (2.7%)	0.380 0.185
The Cornell Voltage Criteria (voltage) Hypertrophic (R aVL + S V3 >35 mm for men, >25 mm for women)	15 (IQR: 13-22) mm 3 (12.5%)	13 (IQR: 9-17) mm 3 (2.7%)	0.054 <b>0.035</b>
<b>Hypertrophic findings at echocardiography (*n=115)</b>	n=16	n=99	<b>0.033</b>
Hypertrophic	9 (56.3%)	29 (29.3%)	
<b>Variables</b>	<b>Yes (n=15)</b>	<b>No (n=120)</b>	<b>p value</b>
<b>Outcome 2: symptomatic intracranial hemorrhage</b>			
<b>Sex</b>			
Female	7 (47%)	46 (38%)	0.582
Male	8 (53%)	74 (62%)	
<b>Age</b>	71.1±11.4	66.7±15.1	0.300
<b>Vital parameters</b>			
Systolic blood pressure (mmHg)	166 (IQR: 155-180)	147 (IQR: 135-160)	<b>0.002</b>
Diastolic blood pressure (mmHg)	100 (IQR: 89-109)	88 (IQR: 80-94)	<b>0.004</b>

Table 3. Continued			
Variables	Yes (n=24)	No (n=111)	p value
<b>Outcome 1: intracranial hemorrhage</b>			
<b>Survey</b>			
Died	6 (40 %)	10 (8%)	<0.001
<b>Electrocardiographic criteria of left ventricular hypertrophy</b>			
The Gubner criteria (voltage)	20 (IQR: 12-28) mm	9 (IQR: 5-13) mm	<b>0.001</b>
Hypertrophic (R I + S III >25 mm)	5 (33%)	6 (5%)	< <b>0.001</b>
The Sokolow -Lyon criteria (voltage)	18 (IQR: 11-21) mm	16 (IQR: 12-24) mm	0.236
Hypertrophic (S V3 + R V5-6 >35 mm)	1 (7%)	4 (3%)	0.521
The Cornell Voltage Criteria (voltage)	20 (IQR: 14-26) mm	13 (IQR: 9-17) mm	<b>0.002</b>
Hypertrophic (R aVL + S V3 >35 mm for men, >25 mm for women)	3 (20%)	3 (3%)	<b>0.002</b>
<b>Hypertrophic findings at echocardiography (*n=115)</b>	n=10	n=105	
Hypertrophic	6 (40%)	32 (27%)	0.281

∗: Patients who underwent echocardiography (number of patients provided), CT: Computed tomography, IQR: Interquartile range

Receiver Operating Characteristic (ROC) Curve Analysis for Predicting Intracranial Hemorrhage Based on Various ECG-LVH Criteria

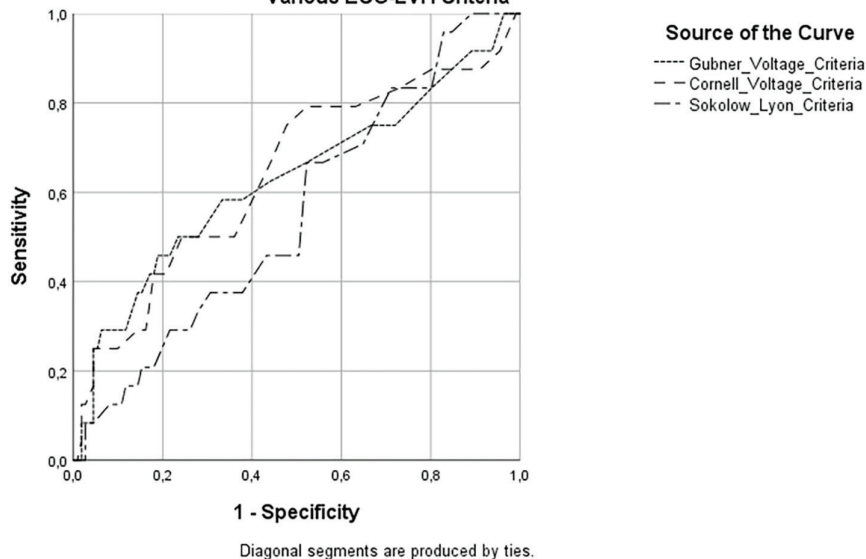


Figure 2. ROC curve analysis of ECG-LVH criteria for predicting any intracranial hemorrhage  
ECG-LVH: Electrocardiogram- left ventricular hypertrophy

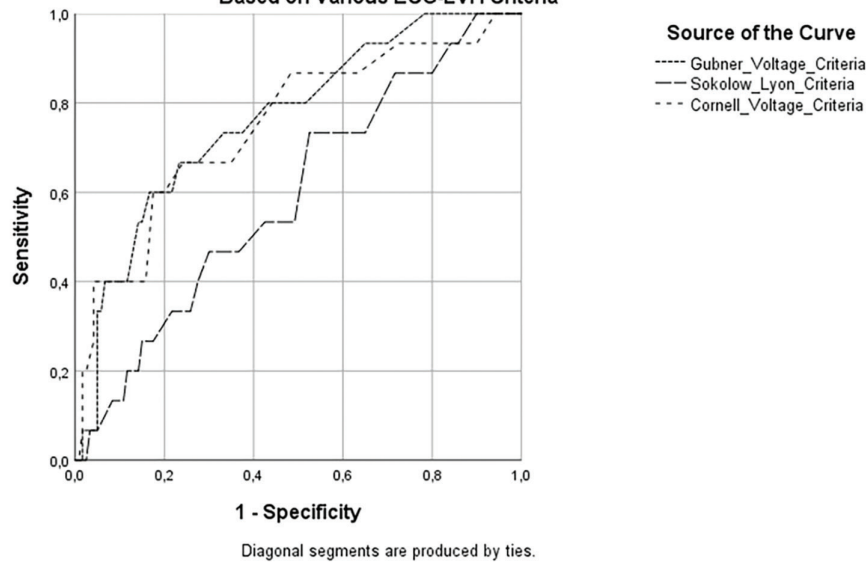
In predicting sICH, both the Gubner and Cornell Voltage Criteria demonstrated statistically significant performance (AUC: 0.764 and 0.751, respectively; both  $p < 0.01$ ) (Figure 3). These AUC values indicate moderate, rather than high, discriminative power. The Gubner criterion achieved 60% sensitivity and 80.8% specificity, while the Cornell criterion demonstrated slightly lower specificity (65.0%) but higher sensitivity (66.7%). The Sokolow-Lyon criterion again yielded nonsignificant results (AUC: 0.594,  $p = 0.237$ ) (Table 4).

Univariable and multivariable logistic regression analyses were conducted to identify independent predictors of sICH. In the

univariable analysis, Gubner voltage [odds ratio (OR): 1.120, 95% CI: 1.045-1.201,  $p = 0.001$ ] and systolic blood pressure (OR: 1.039, 95% CI: 1.012-1.066,  $p = 0.004$ ) were significantly associated with sICH, while age was not ( $p = 0.166$ ).

In the multivariable model, which included Gubner voltage and systolic blood pressure, both remained independent predictors of sICH. Gubner voltage (OR: 1.126, 95% CI: 1.049-1.210,  $p = 0.001$ ) and systolic blood pressure (OR: 1.038, 95% CI: 1.011-1.066,  $p = 0.006$ ) were both independently associated with an increased risk of sICH (Table 5).

**Receiver Operating Characteristic (ROC) Curve Analysis for Predicting Symptomatic Intracranial Hemorrhage Based on Various ECG-LVH Criteria**



**Figure 3.** ROC curve analysis of ECG-LVH criteria for predicting symptomatic intracranial hemorrhage  
ECG-LVH: Electrocardiogram- left ventricular hypertrophy

**Table 4. Predictive performance of electrocardiographic left ventricular hypertrophy criteria for intracranial hemorrhage and symptomatic intracranial hemorrhage**

Outcome 1: Diagnostic performance of ECG criteria for predicting intracranial hemorrhage								
LVH criteria	AUC	95% CI	p value	Best cut off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
The Gubner criteria	0.628	0.491-0.766	<b>0.049</b>	10.5	66.7	47.7	73.3	62.5
Cornell voltage criteria	0.641	0.510-0.773	<b>0.030</b>	14.5	83.3	27	66.7	55.9
Sokolo-Lyon criteria	0.555	0.434-0.676	0.398	13.5	83.3	19.8	70.8	35.1
Outcome 2: Diagnostic performance of ECG criteria for predicting symptomatic intracranial hemorrhage								
The Gubner criteria	0.764	0.640-0.888	<b>0.001</b>	15.5	60.0	80.8	32.0	93.8
Cornell voltage criteria	0.751	0.611-0.891	<b>0.002</b>	15.5	66.7	65.0	28.0	94.5
Sokolow-Lyon criteria	0.594	0.448-0.740	0.237	16.5	53.3	50.8	25.0	90.0

ECG: Electrocardiography, AUC: Area under the curve, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value

**Table 5. Univariable and multivariable logistic regression analysis of factors associated with symptomatic intracranial hemorrhage**

Variable	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	p value
Gubner voltage	1.120 (1.045-1.201)	<b>0.001</b>	1.126 (1.049-1.210)	<b>0.001</b>
Systolic blood pressure	1.039 (1.012-1.066)	<b>0.004</b>	1.038 (1.011-1.066)	<b>0.006</b>
Age	1.034 (0.986-1.085)	0.166		

OR: Odds ratio, CI: Confidence interval

## Discussion

In this study evaluating ECG left ventricular voltage criteria as predictors of ICH and sICH following thrombolytic therapy, in patients with AIS, the Gubner and Cornell Voltage Criteria demonstrated moderate discriminatory power (AUC values around 0.75). Moreover, the RI + SIII (Gubner voltage criterion) was identified as an independent predictor of symptomatic hemorrhage. These findings suggest that ECG-detected LVH showed moderate predictive value and may complement, rather than replace, established predictors.

Both hemorrhagic transformation (HT) and remote ICH following IVT are known to independently increase the risk of poor outcomes (19). Therefore, predicting the occurrence of any type of ICH after IVT is of clinical importance. While some risk factors are shared, distinct predictors have been identified for HT, parenchymal hematoma (PH), and remote ICH. Male sex, a history of prior stroke, OTT, and infarct size have been found to be independent risk factors for HT (20,21). On the other hand, congestive heart failure, advanced age, elevated systolic blood pressure, and atrial fibrillation are known risk factors for PH (22). Pathophysiological mechanisms underlying some of these factors have also been described. For instance, prior research has demonstrated that blood–brain barrier (BBB) permeability increases with age (23). Hypertension may impair vascular elasticity, leading to hyperperfusion injury. Markers of small vessel disease such as cerebral amyloid angiopathy, white matter hyperintensities, and CMB may predict remote ICH through endothelial dysfunction and disruption of the BBB (24,25).

In this context, MARS has been proposed as a potential tool to evaluate the functional consequences of CMBs in AIS patients treated with IVT (26). Since CMBs are often regarded as a consequence of chronic hypertension, their presence may confer predictive value for hemorrhagic complications following IVT. This could explain why mean ECG voltages were found to be significantly higher in patients who experienced post-thrombolytic hemorrhage—whether symptomatic or not—compared to those who did not.

In the current study, no significant difference in LVH was observed between sICH and non-sICH patients based on ECHO findings. However, both the proportion of patients meeting LVH criteria and the mean voltages were significantly higher in the sICH group when assessed using the Gubner and Cornell criteria. While ECHO-LVH reflects anatomical changes in left ventricular wall thickness, ECG-LVH encompasses both anatomical and electrical remodeling (27). Both ECHO-LVH and ECG-LVH have been shown to possess independent prognostic value (28). In our study, the discrepancy between ECG and ECHO-based findings

should be cautiously interpreted and requires further validation, rather than being solely attributed to electrical versus anatomical remodeling.

Assessing LVH using ECG voltage criteria may help improve acute care quality in emergency settings by enabling early prediction of sICH after IVT. Although current guidelines clearly define indications for IVT in AIS patients (29), predicting post-thrombolytic hemorrhage remains a challenge. An increased risk of hemorrhage in patients with CMB has been well documented (30). However, detecting CMBs in the ED MRI, and calculating MARS scores requires radiological expertise, both of which increase time and cost. In contrast, evaluating LVH on ECG is simple, widely accessible, and does not require additional testing. Nevertheless, ECG findings should not be used in isolation for treatment decisions but may be integrated into multiparametric risk models that also include established predictors such as NIHSS, blood pressure, and imaging findings.

In the present study, the Gubner and Cornell Voltage Criteria demonstrated sufficient predictive power for sICH, whereas the Sokolow-Lyon criterion did not perform adequately. Previous research has also shown the superiority of the Cornell and Gubner criteria over the Sokolow-Lyon criterion in predicting sudden cardiac death and detecting anatomical LVH (31,32). Notably, an RI + SIII voltage sum exceeding 15.5 mm was associated with approximately 80% specificity for sICH, suggesting that even patients not formally meeting LVH criteria (e.g., RI + SIII >25 mm) based on Gubner may still carry elevated hemorrhagic risk.

The association between cardiac and cerebral injury appears to stem from the systemic effects of arterial hypertension. Both organs are recognized target of hypertension, as previously demonstrated (33). Consistent with prior studies establishing the prognostic value of LVH in cerebrovascular events (34), our findings indicate that RI + SIII on ECG serves as an independent risk factor for sICH following IVT in AIS patients.

### Study Limitations

This study has several limitations. First, its retrospective design, may have introduced potential bias in data collection and, by nature, is more susceptible to confounding factors. Second, the study was conducted at a single center. However, the center where the study was performed is the largest hospital in the country and serves as a major referral center for AIS patients.

Third, although the Heidelberg Bleeding Classification was used to define hemorrhagic outcomes, comparison with findings in the existing literature may be limited, as some previous studies have utilized different classification systems, such as the European Cooperative Acute Stroke Study (ECASS) II or ECASS

III. Nevertheless, the Heidelberg classification offers a more comprehensive framework than ECASS III, and it has been shown to have good interobserver agreement (35,36).

Fourth, although ECG evaluations were independently performed by three emergency medicine specialists, inter-rater reliability was not assessed, which may limit the robustness of ECG interpretation. Fifth, the relatively small number of sICH cases (n=15) reduces statistical power and limits the generalizability of the findings.

Sixth, although the impact of OTT on post-IVT ICH is well established in AIS, it could not be analyzed in this study due to a lack of data for the majority of patients. Nonetheless, in our hospital, current guideline-based indications for IVT are strictly followed, suggesting that OTT may have had minimal influence on treatment-related complications in our cohort.

Finally, MARS scoring could not be performed in all included patients, which may have influenced the findings related to CMB. However, it is important to note that MRI prior to IVT is not mandatory in the acute stroke setting. Even so, we acknowledge this as a methodological limitation.

## Conclusion

ECG-detected LVH, particularly by the Gubner and Cornell criteria, was associated with sICH after IVT. These findings are hypothesis-generating and suggest that ECG may serve as an adjunct risk marker, but larger, prospective multicenter studies are needed for validation.

## Ethics

**Ethics Committee Approval:** The study was approved by the University of Health Sciences Türkiye, Ankara Etlik City Hospital Ethics Committee (decision no: AEŞH-BADEK-2025-0230; date: 26.02.2025). It was conducted in accordance with the Declaration of Helsinki, and all patient data collected by the researchers were kept confidential.

**Informed Consent:** This was a single-center retrospective study.

## Generative AI Usage Statement

Generative AI and AI-assisted technologies were NOT used in the preparation of this work.

## Footnotes

Surgical and Medical Practices: İ.Ş., Concept: İ.Ş., R.P.K., E.S., Design: İ.Ş., T.S.M., G.Ç.I., N.V.V., M.Y.A., Data Collection or Processing: İ.Ş., R.P.K., E.S., Analysis or Interpretation: İ.Ş., G.Ç.I., Literature Search: İ.Ş., G.Ç.I., Writing: İ.Ş., R.P.K., E.S., T.S.M., G.Ç.I., R.P.K., E.S.

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<b>Supplementary Table 1. Comparison of baseline characteristics, pharmacological therapies, imaging findings, and clinical outcomes between patients who developed intracranial hemorrhage or symptomatic intracranial hemorrhage and those who did not</b>			
<b>Variables</b>	<b>Yes (n=24)</b>	<b>No (n=111)</b>	<b>p value</b>
<b>Outcome 1: Intracranial hemorrhage</b>			
Pharmacological therapies administered			
Antiplatelet therapy	11 (45.8%)	48 (43.2%)	0.817
Anticoagulant therapy	4 (16.7%)	6 (5.4%)	0.056
Antihypertensive therapy	19 (79.2%)	65 (58.6%)	0.059
Alberta stroke program early CT score	8 (IQR: 7.75-10)	8 (IQR: 7-10)	0.178
Modified rankin scale at administration	4 (IQR: 3- 4)	3 (IQR: 3-4)	<b>0.027</b>
Length of hospital stay (days)	12.5 (IQR: 6.5-23)	7 (IQR: 5-12)	<b>0.012</b>
Modified rankin scale at 3rd month	4 (IQR: 3-6)	2.5 (IQR: 1-3)	<b>&lt;0.001</b>
Bridging therapy (mechanical thrombectomy)	5 (21 %)	26 (23%)	0.784
<b>Variables</b>			
<b>Outcome 2: symptomatic intracranial hemorrhage</b>			
Alberta stroke program early CT score	8.5 (IQR: 7-10)	8 (IQR: 6.5-9.5)	0.558
Microbleed anatomical rating scale	6 (IQR:1.5-7.5)	4 (IQR: 2-6)	0.255
Modified rankin scale at administration	4 (IQR: 3.5-4.5)	3 (IQR: 2.5-3.5)	0.305
Length of hospital stay (days)	17.5 (IQR: 4.5-30.5)	8 (IQR: 4-12)	0.075
Modified rankin scale at 3rd month	2.5 (IQR: 1-4)	3 (IQR: 2-4)	<b>0.005</b>
Bridging therapy (mechanical thrombectomy)	4 (27%)	11 (9%)	0,747

CT: Computed tomography, IQR: Interquartile range