# Neutrophil Lymphocyte Ratio (NLR) and Systemic Immune Inflammatory Index (SII) for the Differential Diagnosis of CT-Negative Mild Acute Ischemic Stroke and Transient Ischemic Attack

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# Abstract

**Background:** A number of acute ischemic stroke (AIS) cases may be misdiagnosed as transient ischemic attack (TIA), due to no infarct on initial computed tomography scan and/or mild deficits upon presentation. Several studies have found that neutrophil-lymphocyte ratio (NLR) is an accurate differential diagnostic biomarker for AIS versus TIA; however, no study has evaluated the use of the NLR in differentiating CT negative AIS from TIA. Further, the systemic immune-inflammation index (SII) is a relatively novel immune biomarker that has been shown to be positively correlated with AIS severity, poor functional outcomes and mortality. The purpose of this study is to determine if NLR or SII can be used as a diagnostic biomarker for the differential diagnosis of mild AIS with negative CT upon admission and TIA.

**Methods:** We performed a retrospective medical record review of patients diagnosed with either AIS or TIA. We collected peripheral white blood cell counts within 24 hours of symptom onset and calculated the NLR and SII. Logistic regression was utilized to determine if NLR or SII are significant predictors of CT negative mild AIS.

**Results:** CT negative mild AIS patients were 2 times as likely to have an NLR ³ 2.71 compared to TIA patients, and CT negative mild AIS patients were 2.1 times as likely to have an SII ³595 compared to TIA patients.

**Conclusion:** NLR and SII are easily obtained biomarkers that can be used in early clinical decision making in cases of mild AIS with negative CT scan upon admission.


# Introduction

A number of acute ischemic stroke (AIS) cases may be misdiagnosed as transient ischemic attack (TIA), due to a lack of evidence of infarct on initial computed tomography (CT) scan and/or mild deficits upon presentation. Accordingly, Forster et al. reported that 32% of patients with CT imaging negative for AIS upon initial presentation were found to have acute infarction on subsequent magnetic resonance diffusion-weighted imaging (MR-DWI)[1]. Further, this number may be much higher, as Coutts reported that 60 to 70 percent of AIS cases are initially CT-negative[2].

Given the low sensitivity of CT for the detection of AIS, MR-DWI is considered the gold standard for diagnosis of AIS; however, it is a comparatively slow and expensive process. Therefore, although MR-DWI has a higher sensitivity for diagnosis of AIS, the American Heart Association (AHA) does not recommend the use of MR-DWI in the initial workup or decision for treatment with tissue plasminogen activator (tPA) [3]. Further, AIS diagnosis relies most heavily on clinical presentation, including symptom focality, severity, duration, and past medical history to facilitate rapid diagnosis and treatment. This may be particularly challenging for patients with mild deficits, characterized by National institutes of Health Stroke Scores (NIHSS) ≤ 5 upon initial presentation, as diagnoses of AIS, TIA, and other stroke-mimicking conditions could be considered. TIA is defined as “a transient episode of focal neurological dysfunction

without evidence of acute infarction on neuroimaging"[4]; therefore, by virtue of definition alone, differential diagnosis of AIS versus TIA in patients with focal deficits leading to NIHSS < 5, but no evidence of infarct on initial CT scan remains elusive.

Immune biomarkers have been identified as promising differential diagnostic biomarkers in mild AIS versus TIA. Specifically, several studies have identified neutrophil count, neutrophil percentage, and neutrophil-lymphocyte ratio (NLR) as accurate differential biomarkers for AIS versus TIA[5]–[7]. However, few studies have specifically compared mild AIS and TIA, aside from our group's recent publication by Cavrak et al. (2021), which identified neutrophil percentage as a significant predictor of mild AIS[6]. Specifically, Cavrak et al. reported that the proportion of patients with an elevated neutrophil percentage above normal clinical range (> 60%) was significantly higher in mild AIS compared to both TIA and stroke mimic, with AIS patients 5.3 times more likely to have a neutrophil percentage > 60% at presentation compared to patients with TIA. A major limitation of the Cavrak et al. study was that mild AIS group was not stratified into CT-negative and CT-positive groups. A recent study by Wang et al. (2021) investigated the use of NLR as a biomarker for the diagnosis of AIS in CT-negative patients who presented with non-focal symptoms but were later confirmed as having AIS by MR-DWI, and their results indicated that NLR > 2.35 could diagnose AIS with 78.48% sensitivity and 50% specificity[8].

The systemic immune-inflammation index (SII) is a relatively novel immune biomarker, developed in 2014 by Hu et al., as a prognostic biomarker in patients with hepatocellular carcinoma[9]. SII is a biomarker integrating platelet count, neutrophil count, and lymphocyte count, calculated as platelet count multiplied by NLR (SII = platelet count * (neutrophil count/lymphocyte count). Therefore, an elevated SII can be indicative of a pro-thrombotic state (increased platelet count) and innate versus adaptive immune dysfunction (neutrophilia and/or high neutrophil count with lower lymphocyte counts). To date, a limited number of studies have investigated the use of SII as a prognostic or diagnostic biomarker in AIS. Weng et al. reported that SII levels were higher in AIS patients compared to healthy controls[10]. Additionally, several studies have reported a positive correlation between SII and AIS severity, and that higher SII is associated with poor functional outcome and higher mortality following AIS[10]–[18].

To date, no study has investigated the use of the SII as a diagnostic biomarker between AIS and TIA patients. Therefore, the novel purpose of this study is to: (1) Compare SII levels between AIS and TIA patients and (2) Compare NLR and SII levels between mild CT negative AIS patients and TIA. We hypothesize that both NLR and SII will be higher in AIS compared to TIA patients and can be used as a diagnostic biomarker for the differential diagnosis case of mild AIS with negative CT upon admission and TIA, prior to diagnosis with DWI.

# Methods

This study received ethical approval from the institutional review board at West Virginia University (Protocol # 2007055198). Patient informed written consent was waived.

# Study Population

We performed a retrospective medical record review of patients from 2018–2021 diagnosed with either AIS (ICD10: I63.3, I63.4 or I63.9) or TIA (ICD10: G45).

To be eligible for inclusion in this study, the following criteria were applied: (1) discharge diagnosis of solely AIS or TIA, (2) age ≥ 18 years, (3) known time of symptom onset and presentation to the emergency department (ED) within 24 hours of symptom onset, (4) admission NIHSS ≤ 5, (5) received head CT upon arrival to the ED, (6) received MR-DWI during hospitalization, and (7) had complete blood cell count with differential performed within 24 hours of symptom onset. All patients received an MR-DWI within 36 hours of ED arrival, and AIS cases were confirmed by the presence of infarct on MRI – DWI positive. AIS patients with initial head CT negative for infarct upon admission, but later determined to be AIS with MRI, were grouped as “CT negative AIS”, and AIS patients with infarct visible on initial head CT were grouped as “CT positive AIS”. TIA diagnosis was not initially made by any study investigators; however, one study investigator (AK Adcock, neurologist) corroborated the suspected diagnosis of TIA by confirming the presence of focal stroke-like deficits, but without evidence of infarct on head CT or MRI – DWI negative. Additionally, both AIS and TIA patients were excluded from this study if any of the study variables were missing/incomplete or if any of the exclusion criteria in Table 1 were met.

# Data Collection

Previous medical and medication history was reviewed for all patients for exclusion criteria (Table 1), and the following demographic variables were collected: age, sex, presence of cardiovascular risk factors – heart disease, hypertension, diabetes, hyperlipidemia, atrial fibrillation, smoking, and history of AIS/TIA. The admission NIHSS was recorded, and while many patients had an NIHSS = 0 upon presentation, all patients reported at least one focal deficit at symptom onset. Symptom duration was determined as the elapsed time from symptom onset to ED arrival. Complete white blood cell counts with differential were reviewed to record the following variables: total white blood cell (WBC) count ($10^3$ cells/uL), neutrophil count ($10^3$ cells/uL), neutrophil percentage, lymphocyte count ($10^3$ cells/uL), lymphocyte percentage, and platelet count ($10^3$ cells/uL). The following standard reference ranges were applied to each study variable: WBC [3.7–11 x$10^3$ cells/uL], neutrophil count [1.5–7.7 x$10^3$ cells/uL], neutrophil percentage [≤ 60%], lymphocyte count [1-4.8 x$10^3$ cells/uL], lymphocyte percentage and platelet count [150–400 x$10^3$ cells/uL]. NLR was calculated as the percentage of neutrophils divided by the percentage of lymphocytes (NLR = neutrophil count/lymphocyte count), and SII was calculated as platelet count multiplied by NLR (SII = platelet count * (neutrophil count/lymphocyte count)).

# Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics ® (Version 28) software, and p-values < 0.05 were considered statistically significant. Grubb’s outlier testing was used to detect any significant outliers in all study variables and were removed prior to analysis. The Chi-Square test was used to compare the frequencies of demographic and nominal study variables between groups. For each

continuous variable, the Shapiro-Wilk test was used to test for normality. An independent samples T test or one-way ANOVA was used to detect mean differences for normally distributed immune parameters, and a Mann Whitney U test or Kruskal-Wallis one-way ANOVA was used to detect median differences for non-normally distributed immune parameters

Logistic regression analysis was used to assess for the effect of confounding cerebrovascular risk factors, such as age, gender, and cardiovascular health on each study variable, and forward-conditional logistic regression was used to identify significant predictor variables in logistic regression. Significant variables identified using logistic regression were further analyzed using receiver operating characteristic (ROC), and the optimal cut point based on maximum sensitivity and specificity was determined.

## Results

# Study Population

The medical records of a total of 450 patients were reviewed, and 333 patients met the inclusion criteria for this study. The clinical characteristics from the total study population are presented in Table 2. The only significant difference between mild AIS and TIA patients for the demographic variables presented in Table 2 was baseline NIHSS. Both the median baseline NIHSS (2 vs. 0, $p < 0.0001$) and percentage of patients with a baseline NIHSS = 0 (53% vs. 20%, $p < 0.0001$) were significantly higher in mild AIS patients compared to TIA patients. There was no significant difference in duration of symptoms between mild AIS and TIA patients ($p = 0.154$), nor was duration of symptoms correlated with baseline NIHSS ($R = .025$, $p = 0.654$). *Immune Parameters – Total Mild AIS Versus TIA*

There were several significant differences in immune parameters between mild AIS and TIA patients, as shown in Table 3. While there was no significant difference in total WBC count between mild AIS and TIA, the proportion of mild AIS patients with a WBC count elevated above normal clinical range was significantly greater than TIA (17% vs. 5%, $p = 0.001$). Neutrophil count was significantly higher in mild AIS compared to TIA (5.5 vs. 4.6, $p = 0.001$), as was the proportion of mild AIS patients with neutrophilia ($> 7.7 \times 10^3$ cells/uL) (17 vs. 7%, $p = 0.004$). NLR was also significantly higher in mild AIS compared to TIA (3 vs. 2.5, $p < 0.0001$). There was no difference in platelet count between AIS and TIA ($p = 0.619$); however, SII was significantly higher in AIS patients compared to TIA (683 vs. 516, $p < 0.001$). Additionally, there was no significant difference in duration of symptoms between AIS and TIA ($p = 0.154$), nor was there a significant correlation or effect of symptom duration on any of the immune parameters in Table 3 (data not shown).

Logistic regression was utilized to determine if NLR or SII are significant predictors of AIS. Given the high degree of correlation between the continuous baseline NIHSS variable and percentage of patients with baseline NIHSS = 0, baseline NIHSS = 0 was arbitrarily chosen for logistic regression analysis.

In model 1, NIHSS and NLR were entered into the model, and both NIHSS and NLR remained in the model as significant predictors of AIS. AIS patients were 4.5 times as likely to have an NIHSS > 0 compared to TIA patients (OR = 4.56, 95% CI [2.7–7.5], p < 0.001). Receiver operator characteristics (ROC) analysis was performed determine the NLR value associated with highest sensitivity and specificity or area under the curve. In our dataset, the NLR cut point was determined to be 2.71 (AUC = 0.602), thus NLR ≥ 2.71was also entered into the logistic regression model. AIS patients were 2.1 times as likely to have an NLR ≥ 2.71 compared to TIA patients (OR = 2.11, 95% CI [1.3–3.4], p = 0.002).

In model 2. NIHSS and SII were entered into the model, and both NIHSS and SII remained in the model as significant predictors of AIS. AIS patients were 4.3 times as likely to have an NIHSS > 0 compared to TIA patients (OR = 4.26, 95% CI [2.3–7.7], p < 0.001). Receiver operator characteristics (ROC) analysis was performed determine the SII value associated with highest sensitivity and specificity or area under the curve. In our dataset, the SII cut point was determined to be 595 (AUC = 0.642), thus SII ≥ 595 was also entered into the logistic regression model. AIS patients were 2.4 times as likely to have an SII ≥ 595 compared to TIA patients (OR = 2.36, 95% CI [1.4–3.9], p = 0.002).

Given the significant association between NIHSS and AIS, we split our sample into two groups based on NIHSS –focal deficits (NIHSS 1–5) or non-focal deficits (NIHSS = 0) and to determine if NLR or SII would remain significant predictors of AIS. In model 3, we included only AIS and TIA patients with focal deficits (NIHSS 1–5) and entered NIHSS as a continuous variable and NLR ≥ 2.71 into the model. NIHSS was not a significant predictor of AIS (p = 0.077); however, mild AIS patients were 2.4 times more likely to have an NLR ≥ 2.71 compared to TIA patients (OR = 2.44, 95% CI [1.3–4.3], p = 0.002). In model 4, we included only AIS and TIA patients with focal deficits (NIHSS 1–5) and entered NIHSS as a continuous variable and SII ≥ 595 into the model. Again, NIHSS was not a significant predictor of AIS (p = 0.077); however, mild AIS patients were 2.6 times more likely to have an SII ≥ 595 compared to TIA patients (OR = 2.58, 95% CI [1.4–4.9], p = 0.003). In model 5, we included only AIS and TIA patients with non-focal deficits (NIHSS = 0) and entered NLR into the model. NLR was not a significant predictor of AIS when only including AIS and TIA patients with non-focal deficits (p = 0.269). In model 6, we included only AIS and TIA patients with non-focal deficits (NIHSS = 0) and entered SII into the model. Similar to NLR, SII was not a significant predictor of AIS when only including AIS and TIA patients with non-focal deficits (p = 0.198)

# Immune Parameters – CT Negative Mild AIS Versus TIA

From the total sample of AIS patients, 65 percent were initially CT negative (n = 108), and the clinical characteristics of the CT negative AIS versus TIA patients are presented in Table 4. Again, the only significant difference in CT negative AIS and TIA patients in any of the demographic variables was baseline NIHSS, as both the median baseline NIHSS (2 vs. 0, p < 0.0001) and percentage of patients with a baseline NIHSS = 0 (80% vs. 47%, p < 0.0001) was significantly higher in CT negative AIS patients compared to TIA.

Table 4
Clinical Characteristics – CT Negative Mild AIS Versus TIA

| | **TIA (n = 166)** | **CT Negative AIS (n = 108)** | ***p*-value** |
|---|---|---|---|
| Age (mean years ± SD) | 71 ± 14 | 69 ± 15 | 0.893 |
| Sex (% female) | 53 | 44 | 0.176 |
| Heart Disease (%) | 40 | 35 | 0.342 |
| Hypertension (%) | 78 | 82 | 0.436 |
| Diabetes (%) | 33 | 33 | 0.918 |
| Hyperlipidemia (%) | 52 | 56 | 0.606 |
| Atrial Fibrillation (%) | 15 | 21 | 0.174 |
| Smoking (%) | 39 | 44 | 0.421 |
| Prior stroke/TIA (%) | 22 | 24 | 0.712 |
| Duration of Symptoms (median hours [IQR]) | 4 [8] | 7 [9] | 0.280 |
| Baseline NIHSS (median [IQR]) | 0 [2] | 2 [2] | **0.001** |
| Baseline NIHSS = 0 (%) | 47 | 80 | **< 0.0001** |

Table 5 summarizes the differences in immune parameters assessed in this study between CT negative AIS and TIA patients. The proportion of CT negative AIS patients with a WBC count elevated above normal clinical range was significantly greater than TIA (16% vs. 5%, p = 0.008). Further, the proportion of CT negative AIS patients with a neutrophilia was significantly greater than TIA (15% vs. 7%, p = 0.039). NLR was significantly higher in CT negative AIS patients compared to TIA (3 vs. 2.5, p = 0.032). There was no difference in platelet count between CT negative AIS and TIA (p = 0.901); however, SII was significantly higher in CT negative AIS patients compared to TIA (674 vs. 516, p < 0.001).

Logistic regression was utilized to determine if NLR or SII are significant predictors of CT negative AIS. In model 1, NIHSS and NLR were entered into the model, and both NIHSS and NLR remained in the model as significant predictors of AIS. CT negative AIS patients were 4.2 times as likely to have an NIHSS > 0 compared to TIA patients (OR = 4.23, 95% CI [2.4–7.5], p < 0.001). CT negative AIS patients were 2 times as likely to have an NLR ≥ 2.71 compared to TIA patients (OR = 1.99, 95% CI [1.2–3.4], p = 0.009).

In model 2. NIHSS and SII were entered into the model, and both NIHSS and SII remained in the model as significant predictors of CT negative AIS. CT negative AIS patients were 4.1 times as likely to have an

NIHSS > 0 compared to TIA patients (OR = 4.15, 95% CI [2.1–8.3], p < 0.001). CT negative AIS patients were 2.1 times as likely to have an SII ≥ 595 compared to TIA patients (OR = 2.15, 95% CI [1.2–3.9], p = 0.015).

Given the significant association between NIHSS and AIS, we split our sample into two groups based on NIHSS –focal deficits (NIHSS 1–5) or non-focal deficits (NIHSS = 0) and to determine if NLR or SII would remain significant predictors of CT negative AIS. In model 3, we included only CT negative AIS and TIA patients with focal deficits (NIHSS 1–5), and entered NIHSS as a continuous variable and NLR ≥ 2.71 into the model. NIHSS was not a significant predictor of CT negative AIS (p = 0.257); however, CT negative mild AIS patients were 2.1 times more likely to have an NLR ≥ 2.71 compared to TIA patients (OR = 2.14, 95% CI [1.1–3.9], p = 0.017). In model 4, we included only CT negative AIS and TIA patients with focal deficits (NIHSS 1–5), and entered NIHSS as a continuous variable and SII ≥ 595 into the model. Again, NIHSS was not a significant predictor of AIS (p = 0.890); however, CT negative mild AIS patients were 2.4 times more likely to have an SII ≥ 595 compared to TIA patients (OR = 2.36, 95% CI [1.2–4.9], p = 0.019). In model 5, we included only CT negative AIS and TIA patients with non-focal deficits (NIHSS = 0) and entered NLR into the model. NLR was not a significant predictor of AIS when only including CT negative AIS and TIA patients with non-focal deficits (p = 0.116). In

# Discussion

The purpose of this study was to compare the NLR and SII levels between AIS and TIA patients to determine the if either measure may be valuable in differential diagnosis. First, we compared the NLR and SII levels between our total population of mild AIS patients (CT positive and negative) and TIA. We found that NIHSS, NLR and SII were all significant predictors of mild AIS. Mild AIS patients were 4.5 times as likely to have an NIHSS > 0 compared to TIA patients (OR = 4.56, 95% CI [2.7–7.5], p < 0.001). Mild AIS patients were 2.1 times as likely to have an NLR ≥ 2.71 compared to TIA patients (OR = 2.11, 95% CI [1.3–3.4], p = 0.002). Mild AIS patients were 2.4 times as likely to have an SII ≥ 595 compared to TIA patients (OR = 2.36, 95% CI [1.4–3.9], p = 0.002). This is the first study to demonstrate that SII levels may have value as a differential biomarker between mild AIS and TIA, and this finding likely represents pathophysiological differences between mild AIS and TIA. While this finding is novel from a descriptive and pathophysiological standpoint, this comparison included mild AIS patients that had an infarct visible on initial CT, therefore, a biomarker may lack clinical utility in these patients, since the CT imaging would support the diagnosis of mild AIS without need for an additional biomarker.

Therefore, in the second part of this study, we compared NLR and SII levels between only CT negative mild AIS and TIA. This comparison is more clinically relevant, as mild AIS patients who are initially CT negative may be initially considered TIA due to lack of evidence of infarct prior to obtaining MRI-DWI. In our study, we only included TIA patients who received MRI-DWI to confirm no infarct prior to discharge; however, while not included in this study, during our review, we identified a population of patients diagnosed as TIA, but were discharged without MRI-DWI. Therefore, it is possible that a portion of these patients would have shown signs of infarct on MRI-DWI and be diagnosed as AIS instead of TIA.

Similar to our findings above, we found that CT negative mild AIS patients were 4.2 times as likely to have an NIHSS > 0 compared to TIA patients (OR = 4.23, 95% CI [2.4–7.5], p < 0.001). CT negative mild AIS patients were 2 times as likely to have an NLR ≥ 2.71 compared to TIA patients (OR = 1.99, 95% CI [1.2–3.4], p = 0.009). CT negative mild AIS patients were 2.1 times as likely to have an SII ≥ 595 compared to TIA patients (OR = 2.15, 95% CI [1.2–3.9], p = 0.015).

Last, we split our sample into two groups based on NIHSS –focal deficits (NIHSS 1–5) or non-focal deficits (NIHSS = 0) and to determine if NLR or SII would remain significant predictors of CT negative AIS, and we found that NLR and SII remained as significant predictors of CT negative mild AIS, independent of NIHSS.

While our study yielded novel and potentially clinically valuable information, there are several limitations that should be addressed. First, this study was performed in a relatively small sample, and given this study was the first to compare CT-negative mild AIS and TIA, larger studies should be performed to validate our findings. This is particularly true when our sample was split into two groups based on NIHSS –focal deficits (NIHSS 1–5) or non-focal deficits (NIHSS = 0). This was not the primary objective of our study; however, future studies are warranted to validate the results presented here. Second, while we excluded patients with symptom duration > 24 hours, the temporal dynamics of leukocytes could vary from 0–24 hours of symptom onset. Thus, while there were no significant differences in median symptom duration between study comparison groups, AIS patients presenting nearer to 24 hours of symptom onset compared to more acute presentations may differ in leukocyte profiles. Lastly, as inherent with all studies evaluating TIA, TIA can be considered a negative diagnosis, based on no evidence of infarct, but with at least one focal deficit upon presentation. However, TIA diagnosis may be subjective as negative imaging and focal deficits may also be present in other stroke-mimicking conditions. We attempted to minimize the variability inherent to the diagnosis by only including patients who were evaluated by and diagnosed with TIA by vascular neurologists; however, it is reasonable to assume that our TIA group may include some stroke mimicking cases.

# CONCLUSION

The major implication of this work is that NLR and/or SII levels, in conjunction with medical history and clinical evaluation, may be an additional piece of information that can decrease subjectivity and increase confidence in the differential diagnosis between mild AIS and TIA when initial CT scan is negative. Furthermore, CBC with differential is routinely obtained during initial evaluation of the suspected AIS patient at a low cost and utilizing equipment already available at nearly all emergency departments. The use of CBC with differential may represent a viable addition to timely diagnosis of AIS, especially in rural or underserved facilities with limited access to MRI-DWI.

For the first time, we have shown that the NLR and SII levels may inform clinical decision making by predicting which patients presenting with mild to resolved focal deficits (NIHSS 0–5) are more likely to show definitive evidence of AIS on MRI-DWI. Accurate and timely identification of mild AIS patients has

both acute and long-term implications for clinical management. Lastly, while the purpose of this study was not to challenge current AHA recommendations regarding the use of thrombolytics in patients with mild, non-disabling deficits, it is clear that this AIS subgroup suffers poor long-term clinical outcomes[19]. However, the accurate and expedited identification of mild AIS patients may prove the value of NLR and SII levels to extend beyond diagnosis and into treatment decisions as further research becomes increasingly available.

# Declarations

**Funding:** No funding was received for conducting this study

**Competing Interests:** The authors have no relevant financial or non-financial interests to disclose

**Ethics Approval and Consent:** This study received ethical approval from the institutional review board at West Virginia University (Protocol # 2007055198). Patient informed written consent was waived.

**Data Availability:** Deidentified study data will be made available upon request

**Author Contributions:** All authors contributed to the study conception and design. Specific roles listed below:

**TA Agard –** Study design, data collection, manuscript preparation

**R Hass-** Data collection

**ME Cavrak –** Data collection

**NS Foual –** Data collection

**C Byrum –** Data collection

**AK Adcock –** Study design, clinical adjudication

**D Gehan** – Statistical analysis

**AB Petrone –** Study design, data collection, manuscript preparation

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# Tables

Tables 1-3 and 5 are not available with this version