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Elevated initial blood kynurenine is associated with increased odds of post-stroke infection Kynurenine and post-stroke infection

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Abstract

Objective: Post-stroke infection is a leading cause of acute ischemic stroke mortality. Tryptophan metabolites can modulate the immune response. This study assesses the association between tryptophan metabolism and post-stroke infection.

Methods: Whole blood from the University of Colorado Emergency Medicine Specimen Bank of acute ischemic stroke patients was collected within 72 hours of last known well. Mass spectrometry determined concentrations of tryptophan metabolites. Multivariate logistic regression modeled the association between post-stroke infection within 30 days and metabolite concentrations, controlling for age, sex, NIH stroke scale score, time to sample collection, smoking status, dysphagia, history of chronic kidney or end stage renal disease, and history of diabetes mellitus.

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CRediT authorship contribution statement

Layne Dylla: Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Julie A. Reisz:** Writing – review & editing, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Sharon N. Poisson:** Writing – review & editing, Funding acquisition, Conceptualization. **Paco S. Herson:** Writing – review & editing, Conceptualization. **Lauren H. Sansing:** Writing – review & editing, Formal analysis. **Andrew A. Monte:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jstrokecerebrovasdis.2025.108268.

Results: Of 73 subjects, 21 (28.8 %) developed a post-stroke infection. Those with or without a post-stroke infection had similar concentrations of tryptophan, kynurenic acid and quinolinic acid. Those who developed a post-stroke infection had higher mean concentrations of kynurenine (2.3μM, standard deviation 1.1μM) compared to those who did not develop a post-stroke infection (1.6μM, standard deviation 0.6μM, $p = 0.01$). The adjusted odds ratio of a post-stroke infection within 30 days was 3.94 (95 % Confidence Interval 1.40 – 11.11) for every 1μM increase in kynurenine concentration.

Conclusions: Increasing circulating kynurenine within 72 hours of ischemic stroke onset is associated with increased odds of developing a post-stroke infection within 30 days of emergency department admission. Understanding the causal mechanism of kynurenine promoting post-stroke infection may yield targeted therapeutics that reduce the morbidity and mortality of ischemic stroke.

Keywords

Acute Ischemic stroke; Cerebrovascular infarction; Stroke; Kynurenine; Tryptophan catabolism

Background

Post-stroke infections account for approximately one-third of all stroke deaths, and, among those who survive, are associated with increased hospital length of stay, reduced chance of discharge home, and worse neurological function at 90-days.[1] Attempts to reduce the morbidity and mortality secondary to post-stroke infections have focused on early administration of antibiotics and identifying risk factors for post-stroke infection. These identified risk factors include age, sex, stroke severity, dysphagia, mechanical ventilation, bladder dysfunction, history of diabetes, and history of chronic obstructive pulmonary disorder.[2,3] Most of these factors are not amenable to therapeutic manipulation. Furthermore, meta-analysis of prophylactic administration of antibiotics found that broad antibiotic use may reduce the incidence of post-stroke urinary tract infections, but did not reduce post-stroke pneumonia or improve stroke mortality or neurological outcomes.[4]

Acute infarction resulting in cell death leads to increased inflammation and recruitment of peripheral immune cells to the infarcted tissue within hours afterstroke onset.[5,6] This clears necrotic cells and plays a role in the repair process. It also promotes blood brain barrier dysfunction and a deleterious autoimmune response. Tryptophan metabolism through the kynurenine pathway (Fig. 1) is regulated at multiple stages by pro-inflammatory and immunosuppressive cytokines.[7,8] Additionally, kynurenine, the central metabolite of tryptophan metabolism via the kynurenine pathway, can act as an aryl hydrocarbon receptor ligand and directly modulate the immune response at a cellular level.[9,10]

The kynurenine pathway is upregulated within 24 hours of ischemia onset and results in lower levels of tryptophan and higher levels of kynurenine and other downstream metabolites.[8,11–13] Increased kynurenine to tryptophan ratio is associated with worse neurological outcome and increased infarct volume.[14,15] However, the role of tryptophan metabolism and the kynurenine pathway in post-stroke infections has not been evaluated.

The objective of this study is to characterize concentrations of key kynurenine pathway metabolites in subjects who do and do not develop a post-stroke infection.

Methods

Study population

This is a retrospective study of patients diagnosed by a stroke neurologist with acute ischemic stroke who were enrolled in the University of Colorado Emergency Medicine Specimen Bank. Diagnosis of an ischemic stroke was confirmed on magnetic resonance imaging (MRI) when available.. All subjects were adults, aged 18 years or older who presented to the emergency department (ED) between March 20, 2018, and March 20, 2023 and had a whole blood sample collected within 24 hours of their presentation to the ED which was also within 72 hours of their last known well (LKW). The time between sample collection and LKW was documented.

Subject demographics, comorbidities, treatments, and initial National Institutes of Health Stroke Scale (NIHSS) scores were extracted from the electronic medical record using standardized REDCap data collection forms. The presence of a post-stroke infection was extracted from clinical notes and discharge summaries. Each subsequent clinical encounter that was available within the University of Colorado Health System's electronic health record, including outpatient visits, were reviewed for the 30-day period following initial ED presentation. While the reference window for what is considered a post-stroke infection varies greatly between prior studies, the 30-day window is consistent with prior definitions of "acute" stroke associated pneumonia and is consistent with literature demonstrating that immunosuppression following an acute stroke starts as early as within hours of ischemia and gradually returns to pre-ischemia levels over the following weeks.[16–18] A patient was determined to have a post-stroke infection if the physician documented any of the following: pneumonia, upper respiratory infection, influenza, Covid-19, bacteremia, cellulitis, urinary tract infection, pyelonephritis, sepsis. When possible, supporting data included treatment with antibiotics, the presence of fever, positive upper respiratory viral panel, chest x-ray demonstrating an infiltrate, and/or a urinalysis with pyuria, nitrites and/or leukocyte esterase positivity. The timing of the infection was recorded. The activities of this study and the Emergency Medicine Specimen Bank were approved by the Colorado Multiple Institutional Review Board (COMIRB #21–2515 and COMIRB #17–1642). All work was conducted in accordance with the Code of Ethics of the World Medical Association, Declaration of Helsinki.

Sample collection and tryptophan pathway analysis

Details of the whole blood metabolomic analysis have previously been reported.[19] In brief, whole blood was collected in ethylenediaminetetraacetic acid (EDTA)-coated vacutainers and immediately frozen at −20 °C. For absolute quantification of selected kynurenine pathway metabolites, we thawed individual aliquots on ice. For each sample, 10 μL was diluted with 90 μL of cold 5:3:2 (v/v/v) methanol:acetonitrile:water supplemented with $^{15}N_2$ tryptophan, $^{13}C_{10}$ kynurenine, $^{13}C_6$ kynurenic acid (1 μM each, Cambridge Isotope Laboratories) and $^{13}C_3$,^{15}N quinolinic acid (1 μM, Toronto Research Laboratories). Samples

were vortexed for 30 min at 4°C. We used centrifugation (10 min, 18,000 g, 4°C) to clarify the supernatants. Supernatants were dried under vacuum and resuspended in an equivalent volume of 0.1 % formic acid. Samples were randomized and analyzed on a Thermo Vanquish UHPLC coupled to a Thermo Orbitrap Exploris 120 mass spectrometer with 2 μL injection in positive ion mode using a 5 min C18 gradient as described previously.[20] RawConverter was used to convert data files from .raw to .mzXML. Features were annotated and peaks integrated peaks using Maven (Princeton Univ). Absolute concentrations were determined as previously described.[21]

Statistical analysis

The cohort was characterized using descriptive statistics. All continuous variables failed the Shapiro-Wilk test, suggesting a normal distribution. A students t-test and chi square test compared baseline characteristics among subjects with and without post-stroke infection. Multivariable logistic regression modeled the association between 1μM increase in metabolite concentration and the presence of a post-stroke infection within 30 days, controlling for sex, age, initial NIHSS score, time between LKW and sample collection, smoking status, a history of diabetes mellitus, a history of chronic kidney disease or end stage renal disease, and the presence of dysphagia. While both mechanical ventilation and the presence of a foley are associated with increased risk of post-stroke infection, only one subject had a documented history of both. Thus, the maximum likelihood estimates in the model containing these variables may not exist and the reported odds ratios might be falsely elevated. The same was found for immunosuppression. Immunosuppression, mechanical ventilation and foley use were excluded from the final model. Given the multiple definitions of post-stroke infection, we also performed a secondary analysis in which the definition of a post-stroke infection was limited to within the first 14 days after admission using the multivariable logistic regression model as above. All analyses were performed using SAS v9.4 software (SAS Institute, Cary, NC).

Results

Patient characteristics

Of 73 subjects, 28.8 % (n = 21) developed an infection within 30 days of ED admission (Table 1). Females comprised 57.1 % (n = 12) of those who developed a post-stroke infection, compared to only 42.3 % (n = 22) of those who did not develop a post-stroke infection. In both groups, an acute ischemic stroke was confirmed by magnetic resonance imaging (MRI) in over 90 % of subjects. Only one subject received mechanical ventilation and a urinary foley. This subject developed a post-stroke infection. There were 9.6 % (n = 5) and 28.6 % (n = 6) subjects who developed dysphagia among those who did not and did have a post-stroke infection (p = 0.04), respectively.

Of the subjects with a post-stroke infection, 52.4 % (n = 11) developed a urinary tract infection (confirmed by urinalysis in 7/8 cases) and 23.8 % (n = 5) developed pneumonia (confirmed by chest x-ray in 4/5 cases) (Table 1b). The mean time to infection was 7.9 days (standard deviation [StDev] 8.5 days) from ED admission.

Unadjusted metabolite abundance

The absolute concentrations of tryptophan, kynurenic acid and quinolinic acid were similar among patients who did and did not develop a post-stroke infection within 30 days (Fig. 2). However, the mean concentration of kynurenine among those who did not develop a post-stroke infection (1.6 μM, StDev 0.6 μM, $n = 21$) was significantly lower compared to those who developed a post-stroke infection (2.3 μM, StDev 1.1 μM, $n = 52$; $p = 0.01$).

Adjusted odds ratio of post-stroke infections associated with kynurenine levels within 30 days

Multivariate logistic regression modeled the association between metabolite concentration and the odds of developing a post-stroke infection within 30 days of ED admission, while controlling for: time between LKW and sample collection, factors known to influence metabolite levels (biological sex, age), and factors previously shown to contribute to the development of post-stroke infections (initial NIHSS, smoking status, dysphagia, diabetes mellitus, and chronic kidney disease or end stage renal disease). There was no association between the odds of developing a post-stroke infection and tryptophan (adjusted odds ratio [aOR] 1.00, 95 % Confidence Interval [CI] 0.93 to 1.06), kynurenic acid (aOR 0.64, 95 % CI 0.002 to 233.11), or quinolinic acid concentrations (aOR 1.05, 95 % CI 0.83 to 1.33). The adjusted odds ratio of developing a post-stroke infection within 30 days was 3.94 (95 % CI 1.40 to 11.11) for every 1μM increase in kynurenine concentration.

Association between kynurenine concentration and early post-stroke infections within 14 days

Only 24.7 % ($n = 18$) of subjects developed a post-stroke infection within 14 days of ED admission (Supplemental Table 1). The mean time to infection was 2.6 days (StDev 4.1 days). Subjects who did and did not develop a post-stroke infection had similar unadjusted concentrations of tryptophan, kynurenic acid and quinolinic acid. The mean concentration of kynurenine among those who did not develop a post-stroke infection was 1.6 μM (StDev 0.6μM) and was significantly higher among those subjects who developed a post-stroke infection within 14 days (2.3 μM, StDev 1.2 μM, $p = 0.02$). The aOR of developing a post-stroke infection was 3.3 (95 % CI 1.2 – 9.2) for every 1 μM increase in kynurenine concentration. There was no significant association between tryptophan, kynurenic acid, or quinolinic acid concentrations and the adjusted odds of a post-stroke infection within 14 days of ED admission.

Discussion

This study finds that higher kynurenine concentrations within the first 72 hours of an ischemic stroke are associated with increased odds of developing a post-stroke infection within both the first 30 and 14 days after initial presentation to the ED. However, this study did not find a significant association between post-stroke infection and either concentrations of tryptophan or downstream kynurenine metabolites. This specific association between kynurenine and post-stroke infection has important implications for future tailored therapy to combat post-stroke infections and improve patient outcomes.

The role of kynurenine in immunosuppression after stroke leading to post-stroke infection has not been characterized previously. However, within 24 hours from stroke onset, upregulation of the kynurenine pathway results in lower levels of tryptophan and increased levels of kynurenine and its downstream metabolites.[8,11–13] Kynurenine is the key intermediate metabolite in tryptophan metabolism via the kynurenine pathway (Fig. 1). The conversion of tryptophan to kynurenine by tryptophan 2,3-dioxygenase (TDO) in the liver or by indoleamine 2,3-dioxygenase (IDO) in immune and central nervous system cells is the rate limiting reaction within the kynurenine pathway.[22] Increased levels of kynurenine metabolites, increased IDO activity, and higher ratios of kynurenine to tryptophan are associated with worse neurological function and increased infarct volume.[14,15] Additionally, increased levels of the traditionally “neuroprotective” metabolite, kynurenic acid, are associated with increased 21-day mortality, and lack of early neurological improvement in response to systemic thrombolysis.[13,14,23]

Within hours of stroke onset, the innate immune system is activated leading to increased production of inflammatory cytokines (i.e. interleukin-6 [IL-6] and interferon [IFN]-γ).[24] These cytokines stimulate tryptophan metabolism, increasing activity of both TDO and IDO.[7,8] Increased inflammation upon admission (increased C-reactive protein, erythrocyte sedimentation rates) correlates with increased kynurenine to tryptophan ratios.[11] Increased C-reactive protein levels are also independently associated with post-stroke infection.[25] While kynurenine levels could represent a surrogate inflammatory biomarker, the potential role of kynurenine in stroke likely extends beyond acting as an acute phase reactant. Kynurenine is a ligand for the aryl hydrocarbon receptor and can directly modulate the immune response at a cellular level.[9,10]

Kynurenine binding to the aryl hydrocarbon receptor regulates immune cell differentiation.[7,26] In response to pro-inflammatory cytokines, dendritic cells increase production of kynurenine which in turns binds the aryl hydrocarbon receptor on naïve T cells promoting differentiation into $CD25^{+}FoxP3^{+}$ regulatory T cells and inhibiting differentiation into proinflammatory T-helper-17 cells.[7,9,26,27] In turn, this creates an autoinhibitory loop with decreased production of IFN-γ by both dendritic cells and T cells.[7] Kynurenine can also increase apoptosis of type 1 helper T cells, natural killer cells, and neutrophils; increase production of immunosuppressive cytokines; and inhibit cytokine-mediated upregulation of receptors required for natural killer cell function.[7,28] Therefore, the findings of early increased kynurenine, with the potential activation of the aryl hydrocarbon receptor, represents a novel immunosuppressive pathway that may mediate stroke morbidity and represent a new therapeutic target.

The observed association between kynurenine and post-stroke infection is grounded in the known role of kynurenine in immunosuppression in other contexts. However, other downstream metabolites have also been implicated in modulation of the immune system, including kynurenic acid and quinolinic acid.[29] While it is somewhat surprising that neither were associated with post-stroke infection, the role of these kynurenine metabolites in post-stroke infection may have been diluted given that kynurenine represents a key upstream branch point in the kynurenine pathway and can directly modulate the immune response.

Limitations

This study remains limited by a relatively homogenous sample consisting of mild and moderate strokes with few undergoing acute interventions. Known risks for post-stroke infection include increased stroke severity, dysphagia, and mechanical intervention, which were infrequent events in this population.[30] The study was unable to control for infarct volume or discharge NIHSS score which could impact the risk for post-stroke infection at later timepoints. However, initial NIHSS score was used as a surrogate measure of stroke severity. This approach is consistent with prior studies which sought to identify clinical factors associated with post-stroke infection.[31–34] Subjects undergoing acute thrombolysis or thrombectomy may have reduced stroke morbidity which could influence rates of post-stroke infection. However, there was no significant difference in the proportion of subjects undergoing acute treatment in this cohort. The strength of this study lies in the fact that even after controlling for non-modifiable risk factors, kynurenine remained associated with post-stroke infection. This study is unable to determine if the association between kynurenine and post-stroke infection is direct and/or is mediated by other downstream metabolites. Itis possible that kynurenine is a marker of increased inflammation and concomitant immunosuppression. However, the direct role of kynurenine as a ligand for the aryl hydrocarbon receptor argues for a causative role beyond serving as a biomarker. Essential amino acid metabolism, including tryptophan, is affected by dietary factors. This study was unable to account for dietary confounders; blood was not obtained during fasting. This may influence tryptophan and, consequently, kynurenine levels. However, the lack of significant difference in tryptophan concentrations between those with and without a post-stroke infection argues against dietary differences in tryptophan as a significant confounder. Finally, the primary outcome was post-stroke infection within 30 days of ED presentation. This raises the possibility that unknown confounders could contribute to these post-stroke infections However, most infections occurred early after the stroke and our analysis of only post-stroke infections occurring within 14 days, further supports our conclusion that kynurenine is playing an important role in post-stroke infection.

Conclusion

Increasing kynurenine concentrations measured within 72 hours of last known well are associated with increased odds of a post-stroke infection within 30 and 14 days of admission. Kynurenine modulation represents a potential immunosuppressive target that may be amenable to therapeutic manipulation in stroke and other conditions characterized by immunosuppression. Future studies in stroke are needed to determine the precise mechanism through which kynurenine is associated with post-stroke infections and whether inhibition of kynurenine production might provide a new treatment to prevent post-stroke infection and improve stroke outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of competing interest

The authors report no conflicts of interests. The research leading to these results received funding from the following sources: the Colorado Clinical and Translational Sciences Institute Pilot Grant Award (CO-J-22-13), the NIH Building Interdisciplinary Research Careers in Women's Health K12-HD057022 and the American Heart Association Career Development Award (19CDA34660039). The Emergency Medicine Specimen Bank was supported by National Institutes of Health (NIH) (1R35GM124939). The use of REDCap for this project was supported by NIH/NCATS Colorado CTSA Grant Number UL1 TR002535. Its contents are the authors' sole responsibility and do not necessarily represent official NIH views.

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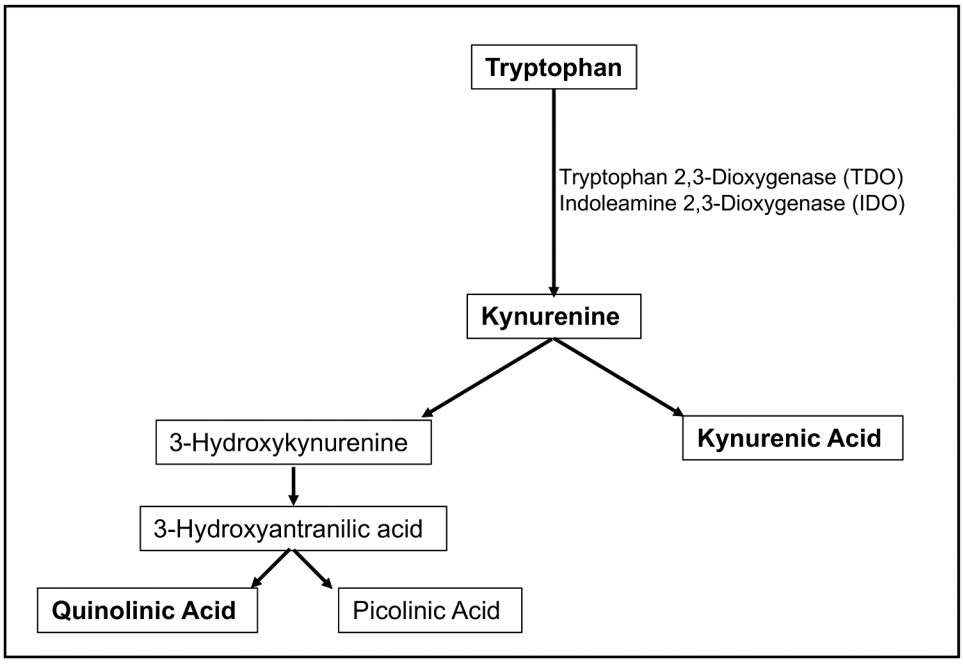
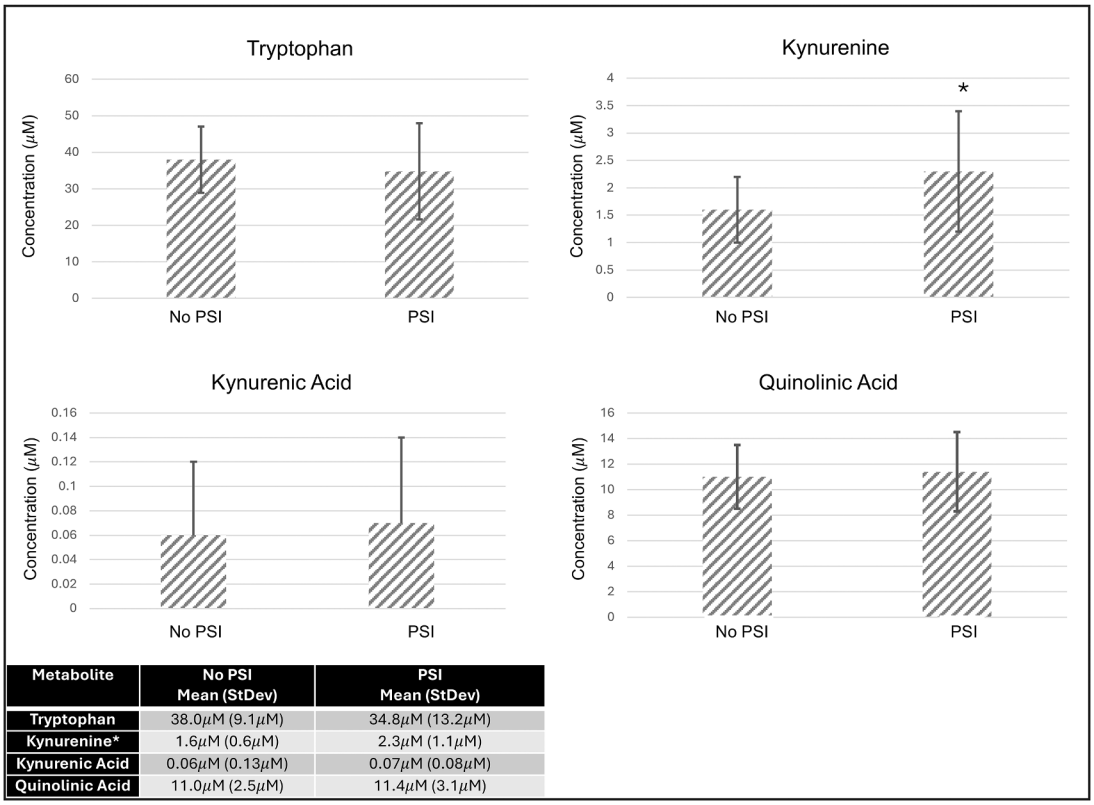


Fig. 1. Tryptophan metabolism via the kynurenine pathway.

Selected downstream kynurenine pathway metabolites included in targeted metabolomic analysis are highlighted in bold.



Metabolite	No PSI Mean (StDev)	PSI Mean (StDev)
Tryptophan	38.0μM (9.1μM)	34.8μM (13.2μM)
Kynurenine*	1.6μM (0.6μM)	2.3μM (1.1μM)
Kynurenic Acid	0.06μM (0.13μM)	0.07μM (0.08μM)
Quinolinic Acid	11.0μM (2.5μM)	11.4μM (3.1μM)

Fig. 2. Mean kynurenine pathway metabolite concentrations in subject who did not and who did develop a post-stroke infection (PSI).

Error bars represent standard deviation. * $p < 0.05$ on student's t-test.

Table 1a

Subject Characteristics.

Subject Characteristic		Overall	No PSI N = 52	Developed PSI N = 21
Age (years) – mean (StDev) [+]		66.4 (12.4)	64.9 (12.1)	72.2 (11.9)
Sex (Females) – n (%)		34 (46.6 %)	22 (42.3 %)	12 (57.1 %)
Race	White	51 (69.9 %)	39 (75.0 %)	12 (57.1 %)
	Black, African American	12 (16.4 %)	8 (15.4 %)	4 (19.1 %)
	American Indian/Alaska Native	1 (1.4 %)	0 (0 %)	1 (4.8 %)
	Other	7 (9.6 %)	4 (7.7 %)	3 (14.3 %)
	UTD	2 (2.7 %)	1 (1.9 %)	1 (4.8 %)
Ethnicity – Hispanic		16(22.5 %)	12 (23.5 %)	4 (20.0 %)
MRI-confirmed stroke		69 (94.5 %)	50 (96.2 %)	19 (90.5 %)
In-hospital interventions	IVT	18 (24.7 %)	15 (28.9 %)	3 (16.7 %)
	EVT	3 (3.0 %)	1 (1.9 %)	2 (9.5 %)
Past Medical History	Immunosuppressed	8 (11.0 %)	5 (9.6 %)	3 (14.3 %)
	HTN	56 (76.7 %)	38 (73.1 %)	18 (85.7 %)
	Dyslipidemia	42 (57.5 %)	28 (53.9 %)	14 (66.7 %)
	Atrial Fibrillation	12 (16.4 %)	9 (17.3 %)	3 (14.3 %)
	Diabetes Mellitus	31 (42.5 %)	24 (46.2 %)	7 (33.3 %)
	CAD or HF	24 (32.9 %)	16 (30.8 %)	8 (38.1 %)
	CKD/ESRD [*]	8 (19.1 %)	4 (7.7 %)	4 (19.1 %)
	Current smoker	9 (12.3 %)	6 (11.5 %)	3 (14.3 %)
	Former smoker	32 (43.8 %)	24 (46.2 %)	8 (38.1 %)
	Never smoker	32 (43.8 %)	22 (42.3 %)	10 (47.6’%)
Initial NIHSS – mean (StDev); median (IQR) [++]		4.2 (5.3); 3 (1–5)	3.2 (3.7); 2 (1–5)	8 (8.2); 6 (58)
Time between LKW and sample collection (hours) – mean (StDev)		21.2 (17.6)	21.7 (17.8)	19.4 (17.3)

[*] chi-square $p < 0.05$

[+] student’s t-test <0.05

[++] student’s t-test $p = 0.05$

Abbreviations: PSI – Post-stroke Infection; StDev – standard deviation; IQR – interquartile range; IVT – intravenous thrombolysis; EVT – endovascular thrombectomy; MV – mechanical ventilation; HTN – hypertension; CAD – coronary artery disease; HF – heart failure; CKD – chronic kidney disease; ESRD – end stage renal disease; LKW – last known well.

Table 1b

Distribution of Infection Type.

Type of Infection *	N (%)
Urinary Tract Infection	11 (52.4 %)
Pneumonia	5 (23.8 %)
Bacteremia	4 (19.0 %)
Other Infection	10 (47.6 %)

* Subjects could have more than one infection type.