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Procalcitonin as a prognostic biomarker for stroke: A systematic review and meta-analysis

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Abstract

Background & Objective: Stroke remains as an important cause of morbidity and mortality worldwide. Despite outcome prediction models available, determining functional outcomes remains a challenge hence there have been an increasing interest in novel prognostic biomarkers for stroke. Several studies have explored the prognostic significance of procalcitonin levels in determining functional outcomes and mortality in stroke patients. This study aims to systematically review articles and to determine if elevated procalcitonin is associated with poor functional outcomes and mortality. *Methods:* Specific search terms were applied in Medline, Cochrane Library, ClinicalTrial.Gov, Global Index Medicus, and Herdin and studies were screened based on the inclusion and exclusion criteria. *Results:* A total of 5 articles were deemed eligible for inclusion and there was no significant heterogeneity among them. Risk of bias was low based on the Quality in Prognostic Studies Tool and no significant bias was detected based on Egger's test (p = 0.3560). Elevated procalcitonin levels were associated with an unfavorable functional outcome (OR 3.76; 95% CI 2.78-5.09) and mortality (OR 3.91; 95% CI 2.80-5.45) at 3 months to 1 year.
Conclusion: The findings of the study demonstrates procalcitonin's potential role as a prognostic biomarker in stroke. Larger studies with broader geographic scope may further strengthen the evidence for procalcitonin's role in stroke prognosis.

Keywords: Functional outcome; Mortality; Procalcitonin; Prognostic biomarker; Stroke

INTRODUCTION

Stroke remains to be an important cause of morbidity and mortality worldwide with a 70% increase in the absolute number of incident cases in the past two decades and with a higher burden of disease among low to middle income countries.[1] Being able to predict outcomes in stroke may guide clinicians and caregivers through the continuum of stroke care, anticipate potential complications, tailor management, and allocate resources effectively.[2] Currently, the most robust predictors of functional outcome and mortality among stroke patients are clinical factors such as stroke severity, subtype, age, sex, and comorbidities[3] and various prognostic models have been developed.[4] Despite these prediction models, determining functional outcomes remains a challenge to clinicians due to the limited predictive value of these scoring systems. It has been proposed that discovery and addition of novel prognostic biomarkers may help improve their prognostic accuracy.[5] Within the last two decades, there has been a 3.5-fold increase in the number of biomarkers for stroke associated with poor outcomes which include cardiac biomarkers, hormones, neurotrophic factors, hemostatic, lipid biomarkers, and inflammatory mediators, one of which is procalcitonin.[6]

Procalcitonin, the 116 amino acid precursor of calcitonin, is classically associated with bacterial infections and sepsis.[7] Apart from infection, procalcitonin has been proposed to have clinical utility in neurology as several studies have shown that patients with acute ischemic stroke tend to have higher procalcitonin values on admission as compared to normal controls.[8-10] And with the recent interest in finding novel biomarkers for stroke, several studies have attempted to determine the prognostic significance of procalcitonin in acute stroke patients with promising results.[8-12] However these studies have small sample sizes and have limitations in the strength of association

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between procalcitonin and stroke outcomes. To date, there have been no previous systematic review or meta-analysis describing the association of procalcitonin levels with functional outcome and mortality. This paper aims to collate findings from previous studies and determine if elevated levels of procalcitonin among patients with acute stroke is associated with poor functional outcomes and mortality.

METHODS

Search strategy

Medline, Cochrane Library, ClinicalTrial.Gov, Global Index Medicus, and Herdin were utilized as the primary databases for this systematic review and meta-analysis for studies published within the inclusive period of January 1, 1980 to June 30, 2024. The following search terms were used: (1) "procalcitonin" AND "stroke" AND "outcome, (2) "procalcitonin" AND "infarct" AND "outcome", (3) "procalcitonin" AND "cerebrovascular" AND "outcome", (4) "procalcitonin" AND "intracerebral" AND "outcome", (5) "procalcitonin" AND biomarker" AND "stroke", and (6) "procalcitonin" AND "prognostic" AND "stroke". Additionally, reference list of the relevant articles was also checked for other potential studies that may be included in the review.

Inclusion and exclusion criteria

Inclusion of studies was based on the following criteria: (1) enrollment of stroke patients > 18 years of age (either ischemic or intracerebral hemorrhage) as participants; (2) in whom baseline procalcitonin levels were measured within the acute phase (within 72 hours) of the stroke; (3) outcomes measured were either functional outcome as defined by the modified Rankin Scale and dichotomized into those with favorable or unfavorable functional outcome, with mRS 0-2 and mRS 3-6 respectively, or survival outcome; (4) the odds ratio with a 95% confidence interval were provided or sufficient data was provided in the article to calculate it with 95% confidence interval. Studies were excluded if (1) the study only indirectly associated procalcitonin with outcomes (e.g. procalcitonin association with stroke-associated pneumonia) (2) study was not written in English, and (3) the full text of the article was not available for review.

The primary investigator and two stroke specialists assessed the title and abstract of studies based on the systematic search for inclusion of the study in this meta-analysis and the final studies to be included in the analysis was determined through consensus. The risk of bias in eligible studies were assessed using the Quality in Prognosis Studies (QUIPS) tool[13] to evaluate six bias domains as high, moderate or low risk of bias based on the parameters considered per domain. The domains include study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting.

Data extraction

Data extracted from the studies included year of publication, country, study design, total number of participants, type of stroke, mean procalcitonin levels obtained or derived and standard deviation, functional outcomes defined through the modified Rankin Scale (mRS), mortality, duration of follow-up, and the corresponding odds ratios (OR) calculated after adjusting for possible and identified confounders.

Statistical analysis

The Rstudio statistical software was used to analyze the data. The odds ratios obtained or derived from the individual studies were used as the effect size in this meta-analysis and a pooled odds ratio and 95% confidence interval was calculated. The prognostic value of procalcitonin was estimated through a forest plot. Heterogeneity among the studies was evaluated using Cochran's Q test and I^2 statistic. A random-effect model was applied to calculate the pooled odds ratio if there was significant heterogeneity among the enrolled studies ($p < 0.05$, or $I^2 > 50\%$). If no significant heterogeneity was observed ($p > 0.05$ or $I^2 < 50\%$), a fixed-effect model was used instead. Publication bias was quantitatively assessed by Egger's Test where a p value < 0.05 was considered significant.

RESULTS

Literature search and screening

A literature search through the databases using the different search terms yielded a total of 127 studies (Figure 1.). Among them 19 were excluded due to duplications and 91had titles that were unrelated to the research question. 17 articles were screened, however 1 study was not written in English hence was excluded, leaving a total of 16 articles for full-text review. 9 articles

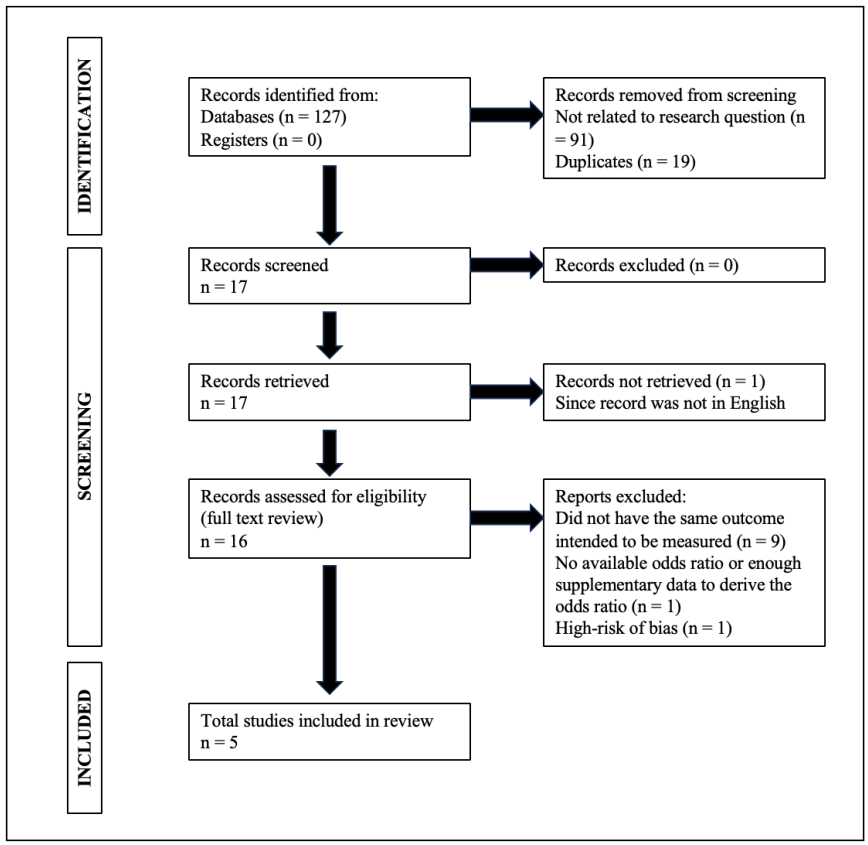

Figure 1. Flow diagram of the study selection process

measured the association of procalcitonin to stroke-associated pneumonia and not directly to functional outcomes or mortality, 1 article did not contain an odds ratio nor had supplementary or raw data from which to derive the odds ratio hence were excluded. Finally, 1 article, although appeared appropriate to be included with the outcomes of interest, was assessed to have a high risk of bias based on the Quality in Prognosis Studies tool[13] due to important missing data such as the number of participants that did not survive, attrition of participants, information on how exactly the outcomes were obtained, and with an inadequate exclusion criteria and was also excluded.

Basic characteristics of included studies

Table 1 shows the basic characteristics of the included studies. All the studies included were single-center studies done in China. The prospective-specimen-collection, retrospective-blinded-evaluation (PRoBE) study design were employed in the 5 studies, which is a design that is used for prognostic factors where clinical information and specimen collection without a priori knowledge on the outcomes to be measured. 4 studies included patients with Acute Ischemic Stroke only while 1 study enrolled patients with intracerebral hemorrhage only. Sample sizes ranged from 173 to 378, with a total number of participants in this study of 1,352 with follow up of functional and/or survival outcomes at either 3 months or 1 year. Measurement of procalcitonin was done within 24 hours of admission across all the included studies. Those that measured functional outcome used the modified Rankin scale (mRS) with similar definitions for favorable and unfavorable outcome, with mRS of 0-2 and 3-6, respectively. As age and NIHSS are currently the most important predictors of outcomes in stroke patients, these were included in calculating adjusted effect sizes in all. Other factors that were used for adjustment were from prior univariate analyses in individual studies. Among studies that included participants with acute ischemic stroke, 3 were able to report thrombolysis rates which ranged from 29.9% to 100%.

Table 1: Baseline characteristics of studies included in the meta-analysis

Author	Year	Country	Study Design	Sample Size	Age Median (IQR)	NIHSS Median (IQR)	Stroke Type	Thrombolysis	Adjusted Factors	Outcome measured
Deng *et al.*[8]	2015	China	PRoBE	378	70 (62-79)	7 (3-11)	AIS	None reported	Age, sex, NIHSS, HS-CRP, Glucose levels, HTN	3-month functional outcome
Li & Liu[9]	2015	China	PRoBE	374	69 (63-79)	10 (6-15)	AIS	29.9%	Age, sex, NIHSS, smoking, glucose, HS-CRP, HCY, TPA-T, infarct volume, TACS	1-year mortality
Wang *et al.*[10]	2016	China	PRoBE	376	69 (63-79)	10 (6-15)	AIS	42.6%	Age, sex, NIHSS, glucose, AF, HS-CRP, TACS	1-year functional outcome and mortality
He *et al.*[12]	2018	China	PRoBE	251	66 (59-73)	NA	ICH	NA	Age, sex, history of stroke, GCS, pneumonia, BG location, ICH volume, IVH, PHE volume, CRP, FBS	3-month functional outcome and mortality
Shi *et al.*[11]	2022	China	PRoBE	173	70 (59-81)	6 (5-9)	AIS	100%	Age, sex, HTN, DM, CHD, AF, COPD, previous stroke, hyperlipidemia, current smoking, current drinking, NIHSS, SBP, OTT, dysphagia, glucose, WBC, HS-CRP	3-month functional outcome and mortality

Abbreviations: IQR, interquartile range; PRoBE, Prospective-specimen-collection, Retrospective-blinded evaluation; NIHSS, National Institutes of Health Stroke Scale; HS-CRP, high-sensitivity C-reactive protein; HTN, hypertension; HCY, homocysteine, TPA-T, tissue plasminogen activator-treated; TACS, Total anterior circulation syndrome; AF, atrial fibrillation; GCS Glasgow Coma Scale; BG, basal ganglia; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; PHE, perihematomal edema; FBS, fasting blood sugar; DM, diabetes mellitus; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; SBP, systolic blood pressure; OTT, onset-to-treatment time; WBC, white blood cell count

Assessment of bias in included studies

All of the studies included had a low risk for bias based on the Quality in Prognostic Studies Assessment Tool (Table 2.). The sample population included and details on recruitment were adequately defined. Exclusion criteria across the different studies were generally similar which took into consideration conditions or circumstances where procalcitonin levels may be elevated except for the study by He *et al*.[12] which did not take into account infection. Measurement of procalcitonin was consistent across all, with extraction within 24 hours from admission and was measured with a validated assay. Determination of specified outcomes in included studies were performed by trained medical students or physicians through a structured interview which could minimize potential variation in assessment of outcomes or through going through medical records. Confounders were adequately accounted for through univariate analyses of baseline characteristics and were used for subsequent adjustment of computed effect sizes. Additionally, Egger's test did not show significant publication bias for studies concerning functional outcome (z value = 0.9230, p = 0.3560) and mortality (z value = 1.6737, p = 0.0942).

Table 2: Assessment of risk of bias in included studies using the Quality in Prognosis Studies (QUIPS) tool

	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome measurement	Study Confounding	Statistical Analysis
Deng *et al.*[8]	LOW	MODERATE	LOW	LOW	LOW	LOW
Li & Liu[9]	LOW	LOW	LOW	LOW	LOW	LOW
Wang *et al.*[10]	LOW	LOW	LOW	LOW	LOW	LOW
He *et al.*[12]	MODERATE	MODERATE	LOW	LOW	LOW	LOW
Shi *et al.*[11]	LOW	LOW	LOW	LOW	LOW	LOW

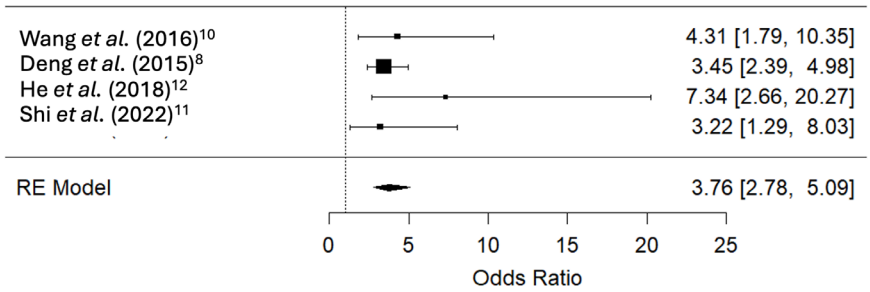

Figure 2. Forest plot showing the odds ratios with 95% confidence intervals of poor functional outcome in stroke patients

Relationship of procalcitonin levels with functional outcome

Among the included studies, 4 measured the functional outcome of stroke patients (1 study on ICH, 3 studies on AIS), collectively with 1,178 participants. All of them had the same definition for favorable and unfavorable functional outcomes based on the modified Rankin Scale, with mRS of 0-2 and 3-6, respectively. The pooled odds ratio is 3.76 (95% CI, 2.78-5.09), as shown in Figure 2. indicating that patients with high procalcitonin levels on admission have a higher odds of having poor functional outcome at 3 months or more after stroke onset. The results among the studies included were consistent and no significant heterogeneity was noted with a Cochran's Q of 2.0825 (p = 0.5555) and I^2 of 0%.

Relationship of procalcitonin levels with mortality

Among the included studies, 4 measured mortality of stroke patients (1 study on ICH, 3 studies on AIS), collectively with 1,174 participants. Of note, the cause of mortality of participants was not determined in all of the studies, and all-cause mortality was measured. The pooled odds ratio is 3.91 (95% CI, 2.80-5.45), as shown in Figure 3. indicating that patients with high procalcitonin levels on admission have a higher odds of dying from any cause after 3 months to 1 year after stroke onset. The results among the studies included were consistent and no significant heterogeneity was noted with a Cochran's Q of 3.3414 (p = 0.3419) and I^2 of 13.49%.

DISCUSSION

Procalcitonin is a widely-used diagnostic test, mainly used for bacterial infections and sepsis. With inflammation being an integral component in the pathophysiology of stroke and the continued interest in improving prediction of outcomes, the utility of procalcitonin in stroke is currently being explored. Our meta-analysis demonstrated that higher procalcitonin levels on admission was associated with poor functional outcome and mortality at 3 months and beyond which supports procalcitonin as a potential prognostic biomarker for stroke. Measurement of procalcitonin, the proposed prognostic factor, and the outcomes were straightforward and consistent in the included studies and the determination of the effect sizes were appropriately adjusted for confounders. There are only limited studies to date that investigated the role of procalcitonin in stroke prognosis. Despite this small number, those included in this meta-analysis did not show significant heterogeneity. However, it is important to note that the studies included were all single-center studies with relatively small sample sizes,

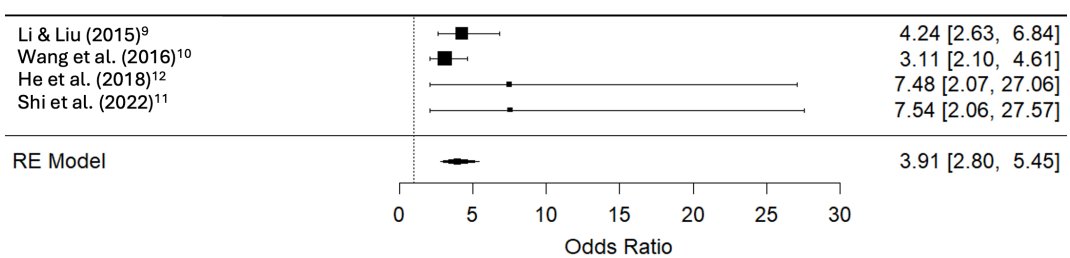

Figure 3. Forest plot showing the odds ratios with 95% confidence intervals of mortality outcome in stroke patients.

and notably, all came from a similar geographic area. In Montellano *et al*.'s[6] systematic review of blood-based biomarkers for stroke prognosis, he commented that the overall quality of prognostic studies in the current literature is poor given the lack of standardization of techniques for acquisition, storage, and reporting of data. Additionally, the statistical power to determine clinical applicability of biomarkers has not yet been agreed upon.[14] This highlights the need for larger studies with a broader geographic scope to strengthen evidence for prognostic utility of procalcitonin in stroke patients as well as an overall improvement in how prognostic studies are conducted.

Apart from bacterial infections, procalcitonin levels may also become elevated in the setting of severe trauma or burns, recent major surgery, prolonged cardiogenic shock, certain paraneoplastic syndromes and may have higher baseline levels on patients with chronic kidney disease.[7] Exclusion criteria of the studies included were able to account for most of these conditions, except those who have severe burns and those who have undergone recent major surgery which were also not included in the baseline characteristics of patients presented in the studies. Nonetheless, an important finding in the included studies was the significant elevation of procalcitonin levels among stroke patients as compared to normal controls and the further increase in procalcitonin with increasing stroke severity through the NIHSS score[8-11] which may provide evidence that acute ischemic stroke itself can lead to elevated procalcitonin levels, considering that patients with infection were excluded from most of the studies. This data however was not available for those with intracerebral hemorrhage. However, the study by He *et al*.[12] was able to show an increase in the odds of developing an unfavorable outcome and mortality in patients with intracerebral hemorrhage with incremental increase in the designated procalcitonin level quartiles after adjusting for confounders.

Although all of the included studies excluded patients with "febrile disorders" and those with "active infection" upon enrollment, only two studies accounted for the eventual development of stroke-associated pneumonia which refers to "the spectrum of pneumonia complicating the first 7 days after stroke onset in non-ventilated patients" as defined by the Pneumonia in Stroke Consensus (PISCES) group.[15] It has been demonstrated that procalcitonin level on admission is also an independent predictor for the occurrence of stroke-associated pneumonia, which in itself, is also a predictor of poor outcomes in stroke.[16] After adjusting for potential confounders for poor outcome, including pneumonia, He *et al*.[12] showed that procalcitonin levels more than 0.054 ng/mL was an independent predictor of unfavorable functional outcome at 3 months and procalcitonin levels more than 0.078 ng/mL was an independent predictor for mortality at 3 months for patients with intracerebral hemorrhage. However, despite excluding febrile patients or patients with active infection, adjustment for pneumonia as a confounder was not performed in studies that enrolled patients with acute ischemic stroke.

Treatment with recombinant tissue plasminogen activator has been demonstrated to improve functional outcomes and decrease mortality in patients treated within 4.5 hours from onset.[17] The proportion of patients with good outcomes that underwent thrombolysis should be considered as an important confounder in the outcomes of interest. One out of the 4 studies that enrolled Acute Ischemic Stroke patients included only those that underwent thrombolysis. For the other 3 studies, two[9,10] reported data on thrombolysis rate (29.9% and 42.6%), but only one[9] of them included thrombolysis in adjusting their effect sizes.

Another important consideration when determining functional outcomes and mortality in stroke is the infarct size. A subgroup analysis was performed for patients that underwent Magnetic Resonance imaging (MRI) in studies conducted by Deng *et al*.[8], Li & Liu[9], and Wang *et al*.[10], and they consistently found that procalcitonin levels paralleled the size of the infarct. After adjusting for lesion size on MRI, elevated procalcitonin levels were still found to be independent predictors of 3-month unfavorable outcome (OR 1.08; 95% CI 1.03-1.13; $p < 0.001$)[8] 1-year unfavorable outcome (OR 2.25; 95% CI 1.55-8.06; $p = 0.002$)[10] and 3-month mortality (HR 1.15; 95% CI 1.06-1.29, $P = 0.009$).[9]

It is well known that stroke triggers an inflammatory cascade that causes both focal and global inflammation that leads to primary and secondary brain injury.[18] MicroRNAs also act as regulators of inflammation through the altered expression in immune cells. Li & Liu[19] proposed a molecular mechanism of how stroke can lead to an increase in procalcitonin levels. They demonstrated that micro-RNAs, specifically miR-637 found in the neuroendocrine cells of the gastrointestinal tract, inhibit the protein translation of procalcitonin. Subsequently, it was

determined that the expression of miR-637 was decreased during acute ischemic stroke which then leads to increased procalcitonin production and secretion. On top of that, production of procalcitonin in parenchymal tissues is mediated by the pro-inflammatory cytokines IL-6, TNF-α and IL-1β[7], all of which are detected within the brain and cerebrospinal fluid in patients with ischemic stroke in animal models[20] and in intracerebral hemorrhage.[21] The pathophysiologic role of procalcitonin in sepsis, more so in stroke still remains uncertain. However, emerging data from experimental studies on human umbilical vein endothelial cells and murine models propose that procalcitonin may dysregulate the function of the endothelial cell barrier, and impair endothelial cell migration and angiogenesis.[22] Furthermore, the proposed endothelial dysfunction associated with procalcitonin may further be aggravated by endothelial dysfunction induced by stroke itself. Stroke impairs endothelium-dependent vasodilation and induces a prothrombogenic endothelial phenotype which contributes to promotion of thrombus formation and reduced blood flow.[23] Endothelial dysfunction in stroke also causes disruption of the blood brain barrier leading to vasogenic edema, accumulation of potentially neurotoxic compounds, and may even result to intracerebral hemorrhage or hemorrhagic transformation of ischemic strokes.[23] These factors may potentially contribute to unfavorable outcomes in stroke patients with elevated procalcitonin levels.

Although a combination of both clinical and laboratory parameters would be optimal, the identification of novel biomarkers for stroke may continuously improve the prognostic accuracy of current predictive models available for stroke. Procalcitonin is already detectable after 1.5 to 3 hours after release of TNF-α and IL-6, peaks at 6-12 hours and with a long-half life of 24 hours.[7] It is a widely-available diagnostic test, easily obtained through blood extraction with no fasting requirement, and is measured by standardized assays, and with immediate results available at point of care. Other important considerations would be feasibility in clinical practice, cost-effectiveness, and whether or not using procalcitonin as a prognostic biomarker will, in fact, translate to actual better clinical decision-making[24], which would require further studies.

This meta-analysis demonstrated that elevated procalcitonin levels on admission is associated with poor functional outcomes and higher mortality, which indicates procalcitonin's potential role as a prognostic biomarker in stroke. However, the results must be interpreted with caution given the limited number of studies available to date and their geographic homogeneity. Larger studies with a broader geographic scope may further strengthen the evidence for procalcitonin's role in stroke prognosis.

DISCLOSURE

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