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Review Article

Blood biomarkers for physical recovery in ischemic stroke: a systematic review

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Abstract: Stroke is a common cause of physical disability. Biomarkers have been used to predict prognosis in ischemic stroke, but studies linking biomarkers to physical recovery from ischemic stroke have not been systematically evaluated since 2011. The purpose of this paper is to report the findings of a systematic review of the intervening literature to identify potential predictive biomarkers for recovery of physical function following ischemic stroke. The PubMed, Embase, and CINAHL databases were searched for studies reported between January 1, 2011, and September 18, 2018. Search criteria were adult ischemic stroke patients, blood sample collection within 24 ± 6 hrs of stroke onset, and outcome measures, including physical function. Identified from 18 studies and representing four biological classifications, 34 biomarkers were significantly associated with physical recovery after ischemic stroke: (1) immune response (15, 44%); (2) lipids/metabolism (4, 12%); (3) neuronal function (4, 12%); and (4) blood vessel/circulation (11, 32%). Of the predictive biomarkers associated with 1-month recovery, 60% (6 of 10) was classified into blood vessel/circulation; 54% (14 of 26) of the biomarkers associated with 3-6 month physical recovery involved the immune response. Blood biomarkers might provide useful information to improve the prediction of physical outcome after ischemic stroke. The data suggest that biomarkers from four biological classifications may predict physical recovery in patients after ischemic stroke.

Keywords: Biomarker, ischemic stroke, recovery of function

Introduction

Stroke is the 5th leading cause of death in the U.S. [1], with an annual incidence of approximately 795,000 cases. Ischemic stroke accounts for 87% of all strokes [1]. In addition, stroke is the most common neurological disease in the adult population worldwide, and the third leading cause of chronic disability [2]. Up to 74% of stroke survivors are dependent in activities of daily living [3].

Motor impairment, sensory dysfunction, and dysphasia are common manifestations of stroke. Up to 30% of stroke survivors in the U.S. suffer permanent disability, and 20% of survivors require inpatient rehabilitation within 3 months after stroke [4]. Improvements in acute stroke care have reduced stroke-related mortality over the past two decades; however, the increased survival rate leaves many survivors with severe disability, placing a tremendous burden on the healthcare system and caregivers [5].

Prior studies indicated that up to 91% of physical recovery occurs within the first 3 months after stroke [6]. Physical recovery includes motor function, sensation, language, and swallowing ability [7]. Because these physical functions often are interdependent, all are included in the assessment of recovery after stroke, and no single measure fully describes disability or functional outcome from stroke.

The most widely used scales for stroke outcomes are the National Institutes of Health Stroke Scale (NIHSS), the modified Rankin Scale (mRS), and the modified Barthel Index (mBI) [8]. The NIHSS is used to quantify stroke

severity based on language, motor function, sensory loss, consciousness, visual fields, extraocular movements, coordination, neglect, and speech [9]. Global disability, with a focus on mobility, is assessed with the mRS [10]. Functional outcomes and daily life activities are measured with the mBI [11]. A statistically significant inverse correlation has been demonstrated between the mRS and the mBI in the post-stroke population [12]; the more disability on the mRS, the less independent the patient scores on the mBI. Furthermore, admission NIHSS score has been found to be positively correlated with mRS score over time [13].

A biomarker is a molecule measured in blood, urine, cerebrospinal fluid, or tissue, or an imaging test, such as magnetic resonance imaging or computed tomography. Blood biomarkers have been commonly used to provide prognostic information following ischemic stroke. For example, levels of brain natriuretic peptide (BNP), D-Dimer, matrix metallopeptidase-9 (MMP-9), and S100B in blood were positively correlated with mortality at 4 months post-stroke [14]. Cardiac markers, such as BNP and troponin, have been shown to have a consistent association with poor outcome after ischemic stroke [15]. Moreover, the most recent systematic review of blood biomarkers for acute stroke found that levels of glucose, glutamate, and fibrinogen at stroke onset were associated with poor prognosis in ischemic stroke patients [16].

Emerging biomarkers from new discoveries in the field of stroke research may help predict stroke outcome and recovery. As the Hasan et al. [16] publication is the most recent and relevant systematic review, the purpose of this review was to synthesize the literature published after 2011 on the relationship between biomarkers and physical recovery from ischemic stroke. Ultimately, biomarkers may provide prognostic information to guide clinicians with patient-centered rehabilitation efforts.

Methods

Search strategy

PubMed, Embase, and CINAHL databases were searched for studies that examined blood biomarkers and functional outcome in patients with ischemic stroke. The hierarchical search strategies and keywords were (1) biomarker, (2) ischemic stroke, (3) physical recovery, and (4) adult (Supplemental Table 1). Duplications were removed from the list, and titles and abstracts of articles retrieved were reviewed for eligibility. All relevant articles from reference lists of each reviewed paper were identified. After screening the abstracts, final eligibility was determined based on the full content of the articles.

Inclusion and exclusion criteria

Inclusion criteria for the selection of articles to include in the review were: (1) primary source of quantitative study in a peer-reviewed journal published in English between January 2011 and September 2018; (2) patients ≥ age 18 years diagnosed with ischemic stroke; (3) biomarkers measured from blood samples within 24 ± 6 hrs of stroke onset; (4) measure(s) of physical outcome (e.g., NIHSS, mRS and/or mBI); and (5) reported the association with physical outcome for each biomarker. Note that the short window, within 24 ± 6 hrs for blood sampling relative to stroke onset, maximizes the predictive potential of the biomarkers to provide time-sensitive prognostic information in the early clinical evaluation of ischemic stroke. Unpublished theses, dissertations, and conference proceedings were excluded.

Study quality appraisal

A code sheet was used to extract information from each article. The information included author(s), year of publication, subjects, time frame of blood draw, biomarker(s), measurement of physical outcomes, and findings [17]. Where more than one cohort was examined within a study, the results for each cohort were extracted separately. Quality of the study was assessed using the modified questionnaire implemented by Whiteley et al. [15] for the stroke population (Supplemental Table 2). These quality components correspond to the sections on study design and assay methods sections of the REporting recommendations for tumor MARKers prognostic studies (REMARK) [18].

Results

Based on the search keywords, 333 studies were identified from PubMed, Embase, and CINAHL. Three more studies were found

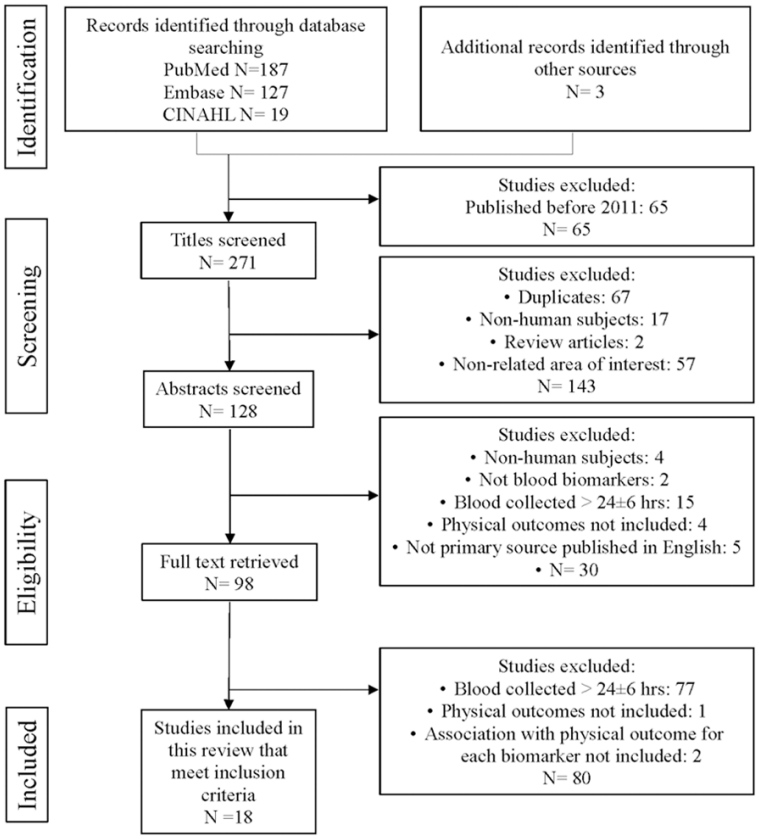

Figure 1. Flow diagram of the literature search. Adapted from "The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration" by Liberati, A. and Altman, D. G., 2009, *British Medical Journal*, 339, b2700.

through Google Scholar and reference lists of relevant articles. The search procedure (**Figure 1**) followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram [19]. After screening the title and abstract of each article, 98 full-text studies were assessed for eligibility; 18 studies met the eligibility criteria and were included in the systematic review.

Characteristics of the studies

The articles are listed in ascending chronological order in Supplemental Table 3. Studies in this review were published between 2011 and 2018. Sample sizes varied from 50 to 783 patients. The proportion of male patients was higher than females (54.3% male vs. 45.7% female). The overall means of patient ages varied from 59 to 73 years. All studies enrolled patients with ischemic stroke, and 5 (28%) included healthy controls as clinical comparisons. Only 2 (11%) of the studies selected patients with first-episode ischemic stroke; the others did not explicitly address history of stroke. Studies were conducted in Spain (7, 39%), Germany (3, 17%), Japan (2, 11%), and 1 (6%) each in the Netherlands, Turkey, the United Kingdom, Poland, the United States, and Italy. Of 73 molecules tested in the 18 studies, 34 (47%) were significantly associated with physical recovery after ischemic stroke.

Methodological assessment

The percentages of reports reviewed that met the modified REMARK criteria for methodological quality are shown in Supplemental Table 4 and **Figure 2**. All study authors defined clinical outcome and provided the characteristics of the study population; 94% used a prospective design; 94% developed a logistic regression model and reported such adjustment variables as age and stroke severity; 72% defined enrollment period; and 67% provided information on the measurement of biomarkers. Few authors reported sample size calculation (6%), and blinded biomarker measurement (33%).

Physical function was defined as an individual's capacity to perform daily personal living tasks like eating, walking, and bathing [20]. A number of outcome measures following ischemic stroke were reported (Supplemental Table 3). Various instruments (NIHSS, mRS, or mBI) were used and outcomes were measured at different time points after stroke (admission, 1, 3, or 6 months). All studies presented NIHSS stroke severity at admission, but only one study reported the 3-month NIHSS score. Therefore, in this review, NIHSS score was not used to define physical recovery from ischemic stroke. In 15 studies (83%), physical outcomes at 3 months were evaluated by mRS or mBI; 2 (11%) and 1 (6%) of the studies reported physical out-

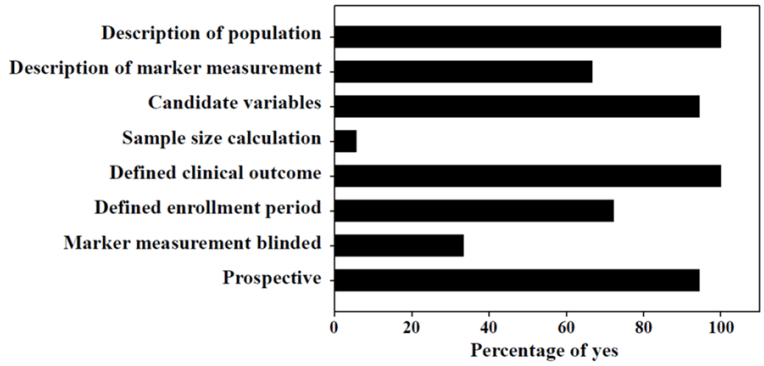

Figure 2. Study quality of the 18 articles in the systematic review assessed by the modified REMARK questionnaire (Supplemental Table 4).

comes at 1 and 6 months after stroke, respectively. Poor outcome was defined according to definitions used in the reviewed articles: mRS ≥ 3 in 13 (72%) studies, mRS ≥ 2 in 2 (11%) studies and mBI < 15 in 1 (6%) study; two studies did not provide cut-off scores for the mRS. Likewise, for this review, we defined physical recovery as used by the authors of the reviewed articles.

Biomarker findings

Biomarkers related to biological functions

The 34 biomarkers that were significantly associated with physical outcome after ischemic stroke were divided into four categories based on biomarker biological function (**Table 1**). In terms of immune response, patients with lower levels of C-C motif chemokine 11 (CCL11), interleukin (IL)-1β and IL-8, and monocyte chemoattractant protein 1 (MCP1) and higher levels of adiponectin, IL-1Ra, IL-6, IL-10, IL-12, copeptin, C-reactive protein (CRP), growth differentiation factor-15 (GDF-15), osteopontin, tumor necrosis factor-alpha (TNFα), and white blood cell (WBC) count at stroke onset showed worse physical recovery (poor outcomes at 1, 3, or 6 months post-stroke). Notably, patients with poor outcome exhibited more than twofold higher levels of copeptin, IL-6, and TNFα compared to those with good outcome.

For lipids/metabolism biomarkers, decreased high-density lipoprotein cholesterol (HDL-C) and increased cholesterol, low-density lipoprotein cholesterol (LDL-C), and glucose at stroke onset were significantly associated with worse functional outcome at 1, 3, or 6 months post-stroke. With respect to biomarkers of neuronal function, patients with ischemic stroke who had higher levels of glutamate and lower levels of glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), and brain-derived neurotrophic factor (BDNF) tended to have worse outcomes at 1, 3, or 6 months after stroke. Patients with poor outcome at 1, 3, or 6 months post-stroke showed increased levels of the blood vessel/circulation biomarkers D-Dimer, endostatin, fibronectin, pro-matrix metalloproteinase-10 (proMMP-10), troponin, and midregional proatrial natriuretic peptide (MR-proANP) and decreased levels of estimated glomerular filtration rate (eGFR), creatinine clearance (CrCl), hematocrit, and hemoglobin at stroke onset. Furthermore, elevated levels of fibrinogen at 1 and 3 months after stroke were associated with poor outcome.

Biomarkers related to physical recovery

Among 34 blood biomarkers that were significantly associated with physical outcome after ischemic stroke (**Table 2**), 10, 26, and 2 biomarkers, respectively, showed a significant association with physical outcome at 1, 3, or 6 months following ischemic stroke: 60% (6 of 10) of biomarkers predictive of physical outcome at 1 month were classified in the blood vessel/circulation category; 54% (14 of 26) of biomarkers that predicted recovery between 3 and 6 months post-stroke were related to the immune response. Elevated levels of CRP and fibrinogen were found to be significant predictors of poor prognosis at 1 and 3 months post-stroke.

Low level of CCL11 and high level of blood glucose were significantly associated with poor outcome at 3 and 6 months after ischemic stroke. Nine (50%) of the reviewed studies reported biomarkers and physical outcomes in patients who had received tissue plasminogen activator (tPA) intravenously, the gold standard treatment of acute ischemic stroke [21]. In this review, patients who received tPA treatment with poor physical outcomes compared to those with good outcomes had higher levels of IL-6, TNFα, osteopontin, fibronectin, endostatin, proMMP-10, CRP, IL-1Ra, IL-10, and IL-12; and

Table 1. Categories of biomarkers significantly associated with physical outcome after ischemic stroke

Category	Biomarker	Article Reference Numbers
Immune response	Adiponectin, CCL11, Copeptin, CRP, GDF-15, IL-1β, IL-1Ra, IL-10, IL-12, IL-6, IL-8, MCP1, Osteopontin, TNFα, WBC	[28-31, 37, 49, 54-57]
Lipids/Metabolism	Cholesterol, Glucose, HDL-C, LDL-C	[30, 31, 37-39, 49, 58]
Neuronal function	BDNF, Glutamate, GOT, GPT	[38, 59]
Blood vessel/Circulation	CrCl, D-Dimer, eGFR, Endostatin, Fibrinogen, Fibronectin, Hematocrit, Hemoglobin, MR-proANP, proMMP-10, Troponin	[29-31, 38, 49, 60]

BDNF = Brain-derived neurotrophic factor; CCL11 = C-C motif chemokine 11; CrCl = Creatinine Clearance; CRP = C-reactive protein; eGFR = Estimated glomerular filtration rate; GDF-15 = Growth Differentiation Factor-15; GOT = Glutamic oxaloacetic transaminase; GPT = Glutamic pyruvic transaminase; HDL-C = High-density lipoprotein cholesterol; IL = Interleukin; LDL-C = Low-density lipoprotein cholesterol; MCP1 = Monocyte chemoattractant protein 1; MMP = Matrix Metalloproteinase; MR-proANP = Midregional proatrial natriuretic peptide; TNFα = Tumor necrosis factor-alpha; WBC = White blood cell.

Table 2. Biomarkers significantly associated with physical outcome after ischemic stroke by time after stroke

Time after stroke	Biomarker associated with physical outcome				Article Reference Numbers
	Immune response	Lipids/Metabolism	Neuronal function	Blood vessel/Circulation	
1 month	CRP, WBC	Cholesterol, LDL-C		CrCl, D-Dimer, Fibrinogen, Hematocrit, Hemoglobin, Troponin	[49, 61]
3 months	Adiponectin, CCL11, Copeptin, CRP, GDF-15, IL-1β, IL-1Ra, IL-6, IL-8, IL-10, IL-12, MCP1, Osteopontin, TNFα	Glucose, HDL-C	BDNF, Glutamate, GOT, GPT	Endostatin, eGFR, Fibrinogen, Fibronectin, MR-proANP, proMMP-10	[28-31, 37, 38, 54-60]
6 months	CCL11	Glucose			[39, 56]

BDNF = Brain-derived neurotrophic factor; CCL11 = C-C motif chemokine 11; CrCl = Creatinine Clearance; CRP = C-reactive protein; eGFR = Estimated glomerular filtration rate; GDF-15 = Growth Differentiation Factor-15; GOT = Glutamic oxaloacetic transaminase; GPT = Glutamic pyruvic transaminase; HDL-C = High-density lipoprotein cholesterol; IL = Interleukin; LDL-C = Low-density lipoprotein cholesterol; MCP1 = Monocyte chemoattractant protein 1; MMP = Matrix Metalloproteinase; MR-proANP = Midregional proatrial natriuretic peptide; TNFα = Tumor necrosis factor-alpha; WBC = White blood cell.

lower levels of HDL, BDNF, IL-1β, IL-8, and MCP1.

Discussion

Of 73 putative biomarkers tested, 34 were found in this review to be statistically significantly associated with physical recovery after ischemic stroke. The biomarkers showed an association with poor outcome by different instruments (mRS or mBI) and measurement time points (admission, 1, 3, or 6 months after stroke). To provide a functional view of the biomarkers, we divided the 34 into four categories based on biological function of the individual biomarker: immune response, lipids/metabolism, neuronal function, and blood vessel/circulation.

Immune response

Brain injury from ischemia is exacerbated by the inflammatory response to cell injury and necrosis [22, 23]. To repair tissue damage, inflammatory cytokines and chemokines attract immune cells from the circulation into the brain [24, 25], and over-activated immune cells adversely augment brain damage leading to an unfavorable recovery [26, 27]. We found that 54% of the 26 biomarkers that predicted long-term (3-6 month) stroke recovery are related to immune response. Consistently, IL-6 [28, 29], TNFα [28, 29], and CRP [28, 30, 31] were found to be robust predictors of long-term functional outcome in ischemic stroke. Therefore, higher levels of immune-related biomarkers after ischemic stroke may reflect worse physical recovery.

Lipids/metabolism

We identified four lipids/metabolism biomarkers (high glucose, cholesterol, HDL-C, and low LDL-C) that were significantly associated with poor outcome after ischemic stroke. High blood glucose, cholesterol, and LDL-C and low HDL-C levels have been associated with increased risk for atherosclerosis and stroke [32-34]. LDL-C and hemoglobin A1c (HbA1c) levels guide recommendations in the American Heart Association/American Stroke Association stroke prevention guidelines [35]. A prior systematic review indicated that low HDL-C level is associated with worse physical outcome after ischemic stroke [36]. Five of the articles [30, 31, 37-39] reviewed in this paper indicated that hyperglycemia was associated with poor outcome in patients with ischemic stroke, which is consistent with previous studies [16, 40, 41]. Hasan et al. [16] reported that admission glucose level might predict poor outcome following tPA treatment; however, the majority of biomarkers we found associated with physical recovery after treatment with tPA were related to immune response and blood vessel/circulation, not to glucose or other biomarkers in the lipids/metabolism category.

Neuronal function

Although different brain regions have different thresholds for ischemic cell damage, neurons are the most sensitive to hypoxia [42]. Glutamate is the major excitatory neurotransmitter in the brain that mediates the signal of neuronal degeneration following ischemic stroke [43, 44]. Elevated levels of glutamate, with decreased GOT and GPT (enzymes to decrease the level of glutamate in peripheral blood), may induce neuronal apoptosis [22, 45]. Higher levels of glutamate, and lower levels of GOT, GPT, and BDNF were associated with less favorable physical recovery after ischemic stroke in this review. Hasan et al. [16] reported similar findings that elevated glutamate may indicate progressive stroke.

Blood vessel/circulation

Ischemia disrupts the mitochondrial membrane potential, which generates excessive reactive oxygen species (ROS) in endothelial cells of cerebral blood vessels [46]. ROS damages mitochondrial DNA, activates the inflammatory response, induces secretion of MMPs, and leads to endothelial cell swelling and death [47]. This process triggers breakdown of the blood-brain barrier and thus increases the risk of hemorrhagic transformation (i.e., bleeding into an area of ischemic brain when cerebral blood flow is restored to damaged vasculature), which adversely affects stroke outcome.

Fibrinogen, an acute phase protein, is involved in platelet activation, coagulation, and hemostasis [48]. Our results support earlier findings that elevated fibrinogen level is associated with poor functional outcome at 1 [49] and 3 months [38] after ischemic stroke. Interestingly, a prior study indicated that an early reduction in

fibrinogen increases the risk of intracerebral hemorrhage after tPA treatment in ischemic stroke patients [50]. Therefore, the relationship between fibrinogen and physical outcome among ischemic stroke patients, with or without tPA intervention, merits further research.

Strengths and weaknesses of the research

A strength of this systematic review is the criterion for timing of blood collection for biomarker determination. The short window-within 24 ± 6 hrs - for blood sampling relative to stroke onset maximizes the predictive potential of the biomarkers to provide time-sensitive prognostic information in the early clinical evaluation of ischemic stroke. Moreover, because stroke recovery is a chronic process, this review addressed potential prognostic prediction of physical recovery at 1, 3, and 6 months after ischemic stroke. Categorization of predictive biomarkers into four broad categories based on biological function may further inform our understanding of the clinicopathology of stroke. On the other hand, the short window for blood collection precluded biomarkers that are expressed in the later phases of ischemic stroke, which may have prognostic importance for physical recovery. Congruent with the prior systematic review [16], high levels of glucose, glutamate, and fibrinogen within 24 ± 6 hrs of stroke onset were repeatedly found to be associated with poor outcome after ischemic stroke.

The review is limited by the information that could not be accounted for because it was either not controlled or not reported in the primary source articles. Biomarker expression typically follows a circadian rhythm. For example, expression of TNFα, IL-1β, and IL-6 is known to peak in the evening [51], whereas copeptin level remains unchanged throughout the 24-hour day [52]. Unknown biomarker expression pattern and/or inconsistency in timing of blood collection within and across studies could have adversely affected the findings. Such issues should be addressed in future prospective studies on biomarker expression after ischemic stroke. Another limitation is the small sample size in some of the eligible studies, which inherently compromises the statistical power of the relationships between blood biomarkers and physical recovery from ischemic stroke.

Implications for clinical practice and future research

The biomarkers we found in the acute period may provide useful insights into prognosis and mechanism(s) of action. These findings can facilitate biomarker-based care in patients with ischemic stroke, and thus match patients with appropriate intervention. A robust number and types of biomarkers have been and continue to be investigated in patients with ischemic stroke. Biomarkers show promise, especially in the prognosis of functional recovery and evaluation of therapeutic response, but the current application of their usefulness in practice is elusive without further research evidence from controlled studies. Future research is expected to align timing of putative predictive biomarker levels with phases of physical recovery; the timing may well correlate with the biological classification of the biomarker and suggest different pathways that are mechanistically different for acute and chronic stroke recovery. For instance, troponin, a blood vessel/circulation marker, indicates myocardial damage in acute coronary syndromes; patients with higher levels of troponin on admission or a peak of troponin measured within 48 hours of a myocardial infarction are likely to have a more difficult and prolonged recovery than patients with lower troponin levels [53].

Prior studies have shown a circadian rhythm influence on cytokine expression [51, 52]. Because 44% of the identified biomarkers in this review are related to immune response; future studies should control the time of day the blood is collected for biomarker determination. Finally, the time of the blood sample collection was constrained to within 24 ± 6 hrs of stroke onset in this review. These early markers may be used in a predictive way to identify subjects at high risk for poor recovery beyond the discharge NIHSS and mRS, so they could be targeted for more aggressive interventions, Additionally, future investigations may extend the time of blood collection to 3 days, 7 days, or even 3 months after stroke to help understand how molecules released in the later response phase correlate with physical outcome after ischemic stroke.

Summary/Conclusions

A systematic review of biomarkers for prediction of stroke recovery has not been updated

since 2011. In the present review, 34 blood biomarkers were significantly associated with physical outcome after ischemic stroke. These biomarkers fall into the biological classifications of immune response, lipids/metabolism, neuronal function, and blood vessel/circulation. The majority of biomarkers appears to predict physical recovery at 3 months following ischemic stroke, with fewer biomarkers predictive of recovery at 1 and 6 months.

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Disclosure of conflict of interest

None.

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Supplemental Table 1. Search Strategies in PubMed, Embase, and CINAHL

PubMed	
Search strategies	Search keywords
(1) Biomarker	("Chemokines"[Mesh] OR "Cytokines"[Mesh] OR "cytokine"[Text Word] OR "cytokines"[Text Word] OR "chemokine"[Text Word] OR "chemokines"[Text Word] OR "Biomarkers"[Mesh] OR "biomarkers"[Text Word] OR "biomarker"[Text Word] OR "Immune Markers"[Text Word] OR "Immune Marker"[Text Word] OR "immunologic Markers"[Text Word] OR "immunologic Marker"[Text Word] OR "blood biomarker"[Text Word] OR "blood biomarkers"[Text Word] OR "serum biomarker"[Text Word] OR "serum biomarkers"[Text Word] OR "plasma biomarker"[Text Word] OR "plasma biomarkers"[Text Word] OR "plasma marker"[Text Word] OR "plasma markers"[Text Word] OR "serum marker"[Text Word] OR "serum markers"[Text Word] OR "blood marker"[Text Word] OR "blood markers"[Text Word] OR "blood indicator"[Text Word] OR "blood indicators"[Text Word] OR "serum indicator"[Text Word] OR "serum indicators"[Text Word] OR "plasma indicator"[Text Word] OR "plasma indicators"[Text Word] OR "plasma factors"[Text Word] OR "plasma factor"[Text Word] OR "serum factors"[Text Word] OR "serum factor"[Text Word] OR "blood factors"[Text Word] OR "blood factor"[Text Word] OR "biological marker"[Text Word] OR "biological markers"[Text Word] OR "biologic marker"[Text Word] OR "biologic markers"[Text Word])
(2) Ischemic stroke	("Cerebrovascular Disorders"[Mesh] OR "Cerebrovascular Disorders"[Text Word] OR "Cerebrovascular Disorder"[Text Word] OR "Cerebrovascular"[Text Word] OR "ischemic stroke"[Text Word] OR "Brain Ischemia"[Text Word] OR "cva"[Text Word] OR "ischemic strokes"[Text Word] OR "stroke syndrome"[Text Word] OR "Brain Ischemia"[Mesh] OR "cerebral vascular accident"[Text Word] OR "cerebrovascular accident"[Text Word] OR "stroke syndromes"[Text Word] OR "cerebrovascular accidents"[Text Word] OR "cerebral vascular accidents"[Text Word] OR "Brain Ischemias"[Text Word] OR "cerebral ischemia"[Text Word] OR "cerebral ischemias"[Text Word] OR "ischemic brain"[Text Word] OR "ischemic brains"[Text Word])
(3) Physical recovery	("Recovery of Function"[Mesh] OR "Recovery of Function"[Text Word] OR "function recovery"[Text Word] OR "function recoveries"[Text Word] OR "physical recovery"[Text Word] OR "physical recoveries"[Text Word] OR "functional recovery"[Text Word] OR "functional recoveries"[Text Word] OR "stroke recovery"[Text Word] OR "motor recovery"[Text Word] OR "motor recoveries"[Text Word] OR "Prognosis"[Mesh] OR "Stroke Rehabilitation"[Mesh] OR "Prognosis"[Text Word] OR "Prognoses"[Text Word] OR "Stroke Rehabilitation"[Text Word] OR "Stroke Rehabilitations"[Text Word]) AND ("severity"[Text Word] OR "disability"[Text Word] OR "mobility"[Text Word] OR "functional independence"[Text Word] OR "physical independence"[Text Word] OR "motor function"[Text Word] OR "motor functions"[Text Word] OR "health outcome"[Text Word] OR "health outcomes"[Text Word] OR "physical outcomes"[Text Word] OR "physical outcome" [Text Word] OR "functional outcomes"[Text Word] OR "functional outcome"[Text Word] OR "motor performance"[Text Word] OR "motor performances"[Text Word] OR "physical function"[Text Word] OR "physical functions"[Text Word])
(4) Adult	("Adult"[Mesh] OR "adult"[Text Word] OR "adults"[Text Word] OR "aged 18 years"[Text Word] OR "age 18 years"[Text Word] OR "aged"[Text Word] OR "elderly"[Text Word] OR "aged 65 years"[Text Word] OR "age 65 years"[Text Word] OR "Aged"[Mesh] OR "working age"[Text Word] OR "working-age"[Text Word] OR "working aged"[Text Word] OR "working-aged"[Text Word])
Embase	
Search strategies	Search keywords
(1) Biomarker	Immune markers':ti,ab,kw OR 'immune marker':ti,ab,kw OR 'immunologic markers':ti,ab,kw OR 'immunologic marker':ti,ab,kw OR 'blood biomarker':ti,ab,kw OR 'blood biomarkers':ti,ab,kw OR 'serum biomarker':ti,ab,kw OR 'serum biomarkers':ti,ab,kw OR 'plasma biomarker':ti,ab,kw OR 'plasma biomarkers':ti,ab,kw OR 'plasma marker':ti,ab,kw OR 'plasma markers':ti,ab,kw OR 'serum marker':ti,ab,kw OR 'serum markers':ti,ab,kw OR 'blood marker':ti,ab,kw OR 'blood markers':ti,ab,kw OR 'blood indicator':ti,ab,kw OR 'blood indicators':ti,ab,kw OR 'serum indicators':ti,ab,kw OR 'serum indicator':ti,ab,kw OR 'plasma indicator':ti,ab,kw OR 'plasma indicators':ti,ab,kw OR 'plasma factors':ti,ab,kw OR 'plasma factor':ti,ab,kw OR 'serum factor':ti,ab,kw OR 'serum factors':ti,ab,kw OR 'blood factors':ti,ab,kw OR 'blood factor':ti,ab,kw OR 'biologic markers':ti,ab,kw OR 'biologic marker':ti,ab,kw OR 'cytokine'/exp OR 'cytokine':ti,ab,kw OR 'cytokines':ti,ab,kw OR 'biomarkers':ti,ab,kw OR 'biomarker':ti,ab,kw OR 'biological markers':ti,ab,kw OR 'chemokine'/exp OR 'chemokine':ti,ab,kw OR 'chemokines':ti,ab,kw OR 'biological marker'/exp OR 'biological marker':ti,ab,kw
(2) Ischemic stroke	Cerebrovascular disease'/exp OR 'cerebrovascular disorders':ti,ab,kw OR 'cerebrovascular disorder':ti,ab,kw OR 'cerebrovascular':ti,ab,kw OR 'brain ischemia'/exp OR 'brain ischemia':ti,ab,kw OR 'brain ischemias':ti,ab,kw OR 'ischemic stroke':ti,ab,kw OR 'ischemic strokes':ti,ab,kw OR 'cva':ti,ab,kw OR 'stroke syndrome':ti,ab,kw OR 'stroke syndromes':ti,ab,kw OR 'cerebral vascular accident':ti,ab,kw OR 'cerebral vascular accidents':ti,ab,kw OR 'cerebrovascular accident':ti,ab,kw OR 'cerebrovascular accidents':ti,ab,kw OR 'brain ischemias':ti,ab,kw OR 'cerebral ischemia':ti,ab,kw OR 'cerebral ischemias':ti,ab,kw OR 'ischemic brain':ti,ab,kw OR 'ischemic brains':ti,ab,kw
(3) Physical recovery	Functional recovery'/exp OR 'prognosis'/exp OR 'stroke rehabilitation'/exp OR 'functional recovery':ti,ab,kw OR 'prognosis':ti,ab,kw OR 'stroke rehabilitation':ti,ab,kw OR 'recovery of function':ti,ab,kw OR 'function recovery':ti,ab,kw OR 'function recoveries':ti,ab,kw OR 'physical recovery':ti,ab,kw OR 'physical recoveries':ti,ab,kw OR 'functional recoveries':ti,ab,kw OR 'stroke recovery':ti,ab,kw OR 'stroke recoveries':ti,ab,kw OR 'motor recovery':ti,ab,kw OR 'motor recoveries':ti,ab,kw OR 'prognoses':ti,ab,kw OR 'stroke rehabilitations':ti,ab,kw AND 'functional independence':ti,ab,kw OR 'disability':ti,ab,kw OR 'severity':ti,ab,kw OR 'mobility':ti,ab,kw OR 'physical independence':ti,ab,kw OR 'motor functions':ti,ab,kw OR 'motor function':ti,ab,kw OR 'health outcome':ti,ab,kw OR 'health outcomes':ti,ab,kw OR 'physical outcomes':ti,ab,kw OR 'physical outcome':ti,ab,kw OR 'functional outcomes':ti,ab,kw OR 'functional outcome':ti,ab,kw OR 'motor performance':ti,ab,kw OR 'motor performances':ti,ab,kw OR 'physical function':ti,ab,kw OR 'physical functions':ti,ab,kw

(4) Adult	Adult'/exp OR 'aged'/exp OR 'adult':ti,ab,kw OR 'adults':ti,ab,kw OR 'aged':ti,ab,kw OR 'elderly':ti,ab,kw OR 'aged 18 years':ti,ab,kw OR 'age 18 years':ti,ab,kw OR 'aged 65 years':ti,ab,kw OR 'age 65 years':ti,ab,kw OR 'working age':ti,ab,kw OR 'working-age':ti,ab,kw OR 'working aged':ti,ab,kw OR 'workingaged':ti,ab,kw

CINAHL

Search strategies	Search keywords
(1) Biomarker	(MH "Biological Markers") OR "Biomarkers" OR "Biomarker" OR "Immune Markers" OR "Immune Marker" OR "immunologic Markers" OR "immunologic Marker" OR "blood biomarker" OR "blood biomarkers" OR "serum biomarker" OR "serum biomarkers" OR "plasma biomarker" OR "plasma biomarkers" OR "plasma marker" OR "plasma markers" OR "serum marker" OR "serum markers" OR "blood marker" OR "blood markers" OR "blood indicator" OR "blood indicators" OR "serum indicator" OR "serum indicators" OR "plasma indicator" OR "plasma indicators" OR "plasma factors" OR "plasma factor" OR "serum factor" OR "serum factors" OR "blood factors" OR "blood factor" OR "biological marker" OR "biological markers" OR "biologic markers" OR "biologic marker" OR (MH "Cytokines") OR (MH "Chemokines") OR "cytokine" OR "cytokines" OR "chemokines" OR "chemokine"
(2) Ischemic stroke	MH "Cerebrovascular Disorders" OR "Cerebrovascular Disorders" OR "Cerebrovascular Disorder" OR "Cerebrovascular" OR "ischemic stroke" OR "Brain Ischemia" OR "cva" OR "ischemic strokes" OR "stroke syndrome" OR "cerebral vascular accident" OR "cerebrovascular accident" OR "cerebrovascular accidents" OR "stroke syndromes" OR "cerebral vascular accidents" OR (MH "Cerebral Ischemia") OR "Brain Ischemias" OR "cerebral ischemia" OR "cerebral ischemias" OR "ischemic brain" OR "ischemic brains"
(3) Physical recovery	"Recovery of Function" OR "function recovery" OR "function recoveries" OR "physical recovery" OR "physical recoveries" OR "functional recovery" OR "functional recoveries" OR "stroke recovery" OR "motor recovery" OR "motor recoveries" OR MH "Prognosis" OR "Prognosis" OR "Prognoses" OR "Stroke Rehabilitation" OR "Stroke Rehabilitations" AND "severity" OR "disability" OR "mobility" OR "functional independence" OR "physical independence" OR "motor function" OR "motor functions" OR "health outcome" OR "health outcomes" OR "physical outcome" OR "physical outcomes" OR "functional outcomes" OR "functional outcome" OR "motor performance" OR "motor performances" OR "physical function" OR "physical functions"
(4) Adult	(MH "Adult") OR "Adult" OR "adults" OR (MH "Aged") OR "Aged" OR "aged 18 years" OR "age 18 years" OR "elderly" OR "aged 65 years" OR "age 65 years" OR "working age" OR "working-age" OR "working aged" OR "working-aged"

These four search strategies were combined as follow: (1) and (2) and (3) and (4).

Supplemental Table 2. REMARK Quality Questionnaire

Item		Yes	No
1	Was the study prospective?		
	YES: The study reported that patients and blood samples were collected prior to the development of an outcome		
	NO: No report or clearly retrospective (e.g. patients with poor prognosis collected prior to biomarker measurement)		
2	Was the evaluation of prognostic marker blinded to patient outcome?		
	YES: The study reported an attempt to blind the person measuring the level of biomarker to patient outcome		
	NO: There was no such report		
3	Was there a defined time period during which patients were enrolled?		
	YES: Study defined time period, end of follow up period and median follow up time		
	NO: Did not define above criteria		
4	Were there precisely defined clinical outcomes at the beginning of the study?		
	YES: Study defined which clinical endpoints are to be measured		
	NO: No such definition		
5	Did the study provide a rationale for study sample size?		
	YES: Evidence of a sensible sample size calculation (e.g. 10 outcomes/variable in a multiple regression model)		
	NO: No attempt to define sample size		
6	Did the study provided a list of candidate variables?		
	YES: A list of variables to be considered in multiple regression analysis were provided at the beginning of the study		
	NO: Evidence that variables were measured and not reported		
7	Were the methods for measuring the prognostic marker adequately described and referenced?		
	YES		
	NO		
8	Were the characteristics of the study patients described?		
	YES: The study described the source and inclusion and exclusion criteria		
	NO: Did not provide the information or it was unclear description		

REMARK = REporting recommendations for tumour MARKer prognostic studies. Modified from "Blood markers for the prognosis of ischemic stroke: A systematic review" by Whiteley et al., 2009, *Stroke*, 40(5), e380-389.

Supplemental Table 3. Characteristics of Studies that Examined the Blood Biomarkers on Physical Recovery in Ischemic Stroke

Author, year	Sample collection Country, year	Cohort	Patient number (male %)	Patient age (mean ± SD)	Blood biomarkers	Outcome measures (time point)		Results: blood biomarker levels according to functional outcomes
						Disability	Severity	
Navarro-Sobrino et al., 2011 [1]	Spain	Healthy controls vs Ischemic stroke (with tPA treatment)	26 (46.2%) vs 109 (55%)	69 ± 9.5 vs 70.9 ± 15.1	*Endostatin SDF-1 HCG KGF HGF TSP-1 TSG-1 VEGF VEGF-R2 PDGF-BB PDGF-AA Angiostatin	mRS (3 M)	NIHSS (Admission, 1 h, 2 h, 12 h, 24 h, 48 h and discharge)	1. Higher endostatin is associated with poor outcome (mRS ≥ 3). 2. Lower KGF/endostatin, KGF/TSP-1, and VEGF-R2/TSP-1 are associated with worse severity (admission). 3. Lower KGF/TSP-1 and VEGF-R2/TSP-1 are associated with worse severity (1 h). 4. Lower HCG, HCG/endostatin, KGF/endostatin, KGF/TSP-1, VEGF, PDGF-BB/Angiostatin, PDGF-AA/TSG-1, VEGF/TSP-1, VEGF/endostatin, VEGF-R2/TSP-1, and HGF/Angiostatin are associated with worse severity (2 and 12 h). 5. VEGF, PDGF-BB/Angiostatin, PDGF-AA/TSG-1, VEGF/endostatin, and HGF/Angiostatin are associated with worse severity (24 h). 6. VEGF, PDGF-BB/Angiostatin, and VEGF/endostatin are associated with worse severity (48 h and discharge).
Mendioroz et al., 2011 [2]	Spain, Dec. 2006-June 2008	Healthy controls vs Ischemic stroke (with tPA treatment)	40 (46.2%) vs 178 (52.8%)	71.5 ± 13.4 vs 71.91 ± 8.1	*Osteopontin Glucose	mRS (3 M)	NIHSS (Admission)	1. Higher osteopontin is associated with poor outcome (mRS ≥ 3). 2. No relationship between glucose and stroke disability (mRS ≥ 3). 3. No relationship between osteopontin and stroke severity.
Brea et al., 2011 [3]	Spain, Feb. 2009-Aug 2009	Ischemic stroke	110 (58.2%) mRS < 3: 48 mRS ≥ 3: 62	74.6 ± 9.8 mRS < 3: 71.9 ± 8.9 mRS ≥ 3: 72.9 ± 10.9	*Glucose WBC Platelets Fibrinogen *CPR TLR3 TLR7 TLR8 TLR9	mRS (3 M)	NIHSS (Admission, 24 h, 72 h, 7 days, 3 M)	1. Higher glucose and CRP are associated with poor outcome (mRS ≥ 3). 2. TLR3, 7, 8, and 9 are not associated with stroke disability.
Campos et al., 2011 [4]	Spain	First episode of ischemic stroke	365 (57.5%) mRS < 3: 168 mRS ≥ 3: 197	70.5 ± 11.4	*Glucose WBC Platelets *Fibrinogen *Glutamate *GOT *GPT	mRS (3 M)	NIHSS (Admission)	1. Higher glucose, fibrinogen, and blood glutamate are associated with poor outcome (mRS ≥ 3). 2. Lower GOT and GPT are associated with poor outcome (mRS ≥ 3).
Groschel et al., 2012 [5]	Germany, Mar. 2009-Feb. 2010	Ischemic stroke	264 (55.3%)	70.3 ± 12.7	*GDF-15 WBC CRP Cholesterol LDL-C HDL-C Triglyceride	mRS (3 M)	NIHSS (Admission)	1. Higher GDF-15 is associated with poor outcome (mRS ≥ 2). 2. Higher GDF-15 is associated with worse severity.

Makihara et al., 2012 [6]	Japan, Oct. 2005-July 2008	Ischemic stroke with tPA treatment	489 (65%) mRS < 2: 188 mRS ≥ 2: 301	70.8 ± 11.6	Total cholesterol *HDL-C LDL-C Triglyceride	mRS (3 M)	NIHSS (Admission)	1. Lower HDL-C is associated with poor outcome (mRS ≥ 2).
Delgado et al., 2012 [7]	Spain	Healthy controls vs Ischemic stroke with tPA treatment	135 vs 99 (51%)	72	Lp-PLA2 mass Lp-PLA2 activity	mRS (3 M)	NIHSS (Admission)	1. Neither Lp-PLA2 mass or Lp-PLA2 activity is not associated with stroke severity. 2. No differences were found in either Lp-PLA2 mass or activity according to the third month.
Rodriguez et al., 2013 [10]	Spain	Healthy controls vs Ischemic stroke (with vs without tPA)	With tPA: 76 (58%) Without tPA: 202 (54%)	With tPA: 66.9 ± 11.3 Without tPA: 73.5 ± 11.3	MMP9 *proMMP-10 TIMP-1 *C-Fibronectin *IL-6 *TNFα	mRS (3 M)	NIHSS (Admission, 24 h, 48 h)	1. ProMMP-10, C-Fibronectin, IL-6, and TNFα are significantly higher in tPA treated patients with poor outcome (mRS ≥ 3). *proMMP-10 is significantly higher in non-tPA treated patients with poor outcome (mRS ≥ 3).
Luitse et al., 2013 [8]	Netherlands, Jan. 2007-June 2008	Ischemic stroke (NG vs HG)	Total: 80 NG: 47 (58.8%) HG: 33 (41.3%)	NG: 59 ± 15.3 HG: 69 ± 10.9	*Glucose	mRS (6 M)	NIHSS (Admission)	1. Hyperglycemia is associated with poor outcome (mRS ≥ 3). 2. Hyperglycemia is associated with worse severity (no statistics data).
De Marchis et al., 2013 [9]	Germany and Switzerland, Mar. 2009-Apr. 2011	Ischemic stroke	Total: 783 Without tPA: 465 (59.4%) With tPA: 318 (40.6%)	71.0 (60.6-80.0)	*Copeptin *Glucose *CRP Creatinine *eGFR	mRS (3 M)	NIHSS (Admission)	1. Higher copeptin, glucose, and CRP are associated with poor outcome (mRS ≥ 3). 2. Lower eGFR is associated with poor outcome.
Selçuk et al., 2014 [11]	Turkey, May 2011-Oct. 2011	Ischemic stroke	50 (48%)	68 ± 13	*S100B	mRS (discharge, 1 M)	NIHSS (1st, 2nd, 3rd day)	1. The first day S100B level is not associated with post-stroke disability at 1 month. 2. There was a poor correlation between functional outcome at 1-month post-stroke and the third day S100B level. 3. No correlation between stroke severity and S100B level.
Potpara et al., 2014 [12]	UK	Ischemic stroke	240 (57.9%)	70.0 ± 8.9	*CRP *Fibrinogen *Cardiac TnI *D-dimer *WBC *CrCl *Total cholesterol HDL-C *LDL-C *Hematocrit Hemoglobin	mRS (1 M)	-	1. Higher CRP, fibrinogen, cardiac TnI, D-dimer, WBC, LDL, and total cholesterol are associated with poor outcome (mRS ≥ 3). 2. Lower CrCl and hematocrit are associated with poor outcome.
Kuwashiro et al., 2014 [13]	Japan, Nov. 2007-Apr. 2010	Healthy controls vs Ischemic stroke	342 (67.3%)	68.3 ± 10.1	*Adiponectin	mRS (3 M)	NIHSS (Admission)	1. Higher adiponectin is associated with worse severity and poor outcome (mRS ≥ 3).

Bustamante et al., 2014 [14]	Spain, Mar. 2003-Nov 2005	Ischemic stroke (with tPA treatment)	159 (55.3%)	70.1 ± 11.4	ChT	mRS (3 M)	NIHSS (Admission, 48 h)	1. ChT activity is not related to baseline stroke severity. 2. Higher ChT activity is associated with poor outcome (mRS ≥ 3), but ChT activity is not an independent predictor.
Lasek-Bal et al., 2015 [15]	Poland, June 2014-April 2015	First episode of ischemic stroke (with tPA treatment)	87 (51.7%)	71.7 ± 11.8	*BDNF	mRS (2 W, 3 M)	NIHSS (Admission)	1. Lower BDNF is associated with poor outcome at 3 months post-stroke (mRS ≥ 3).
Roy-O'Reilly et al., 2017 [16]	USA, 2011-2015	Ischemic stroke	133 (57.1%)	70.42 ± 13.87	*CCL11	mRS and mBI (in-hospital, 3 M, 12 M)	NIHSS (Admission)	1. Lower CCL11 is associated with poor outcome at 3 months (mBI ≤ 14) and 12 months (mRS ≥ 3) post-stroke.
Gori et al., 2017 [17]	Italy, Oct. 2008-June 2011	Ischemic stroke (with tPA treatment)	327 (58.1%)	68.9 ± 12.1	*IL-1β *IL-1RA IL-4 *IL-6 *IL-8 *IL-10 *IL-12 IL-17 IFNγ IP10 *MCP1 MIP1β *TNFα, *CRP A2M SAP Haptoglobin MMP1, 2, 3, 7, 8, and 9 TIMP1, 2, and 4	mRS (3 M)	NIHSS (Admission)	1. CRP, IL-1β, IL-1Ra, IL-6, IL-8. IL-10, IL-12, TNFα, and MCP1 (Pre-post tPA) were associated with three-month (mRS ≥ 3).
De Marchis et al., 2018 [18]	Germany and Switzerland, Mar. 2009-Apr. 2011	Ischemic stroke	Total: 783 Without tPA: 465 (59.4%) With tPA: 318 (40.6%)	71 (61-80)	*MR-proANP *Glucose *CRP *eGFR	mRS (3 M)	NIHSS (Admission)	1. Higher MR-proANP, glucose, and CRP are associated with poor outcome (mRS ≥ 3). 2. Lower eGFR is associated with poor outcome.

A2M = Alpha-2-Macroglobulin; BDNF = Brain-derived neurotrophic factor; CCL11 = C-C motif chemokine 11; ChT = Chitotriosidase; CrCl = Creatinine Clearance; CRP = C-reactive protein; eGFR = Estimated glomerular filtration rate; GDF-15 = Growth Differentiation Factor-15; GOT = Glutamic oxaloacetic transaminase; GPT = Glutamic pyruvic transaminase; h = hour(s); HDL-C = High-density lipoproteins cholesterol; HG = Hyperglycaemia; HGF = Hepatocyte growth factor; IFNγ = Interferon gamma; IL = Interleukin; IP10 = Interferon gamma-induced protein 10; KGF = Keratinocyte growth factor; LDL-C = Low-density lipoproteins cholesterol; Lp-PLA2 = Lipoprotein-associated phospholipase A2; M = month(s); mBI = modified Barthel index; MCP1 = Monocyte chemoattractant protein 1; MIP1β = Macrophage inflammatory protein-1β; MMP = Matrix Metalloproteinase; MR-proANP = Midregional proatrial natriuretic peptide; mRS = modified Rankin score; NG = Normoglycaemia; NIHSS = National Institutes of Health Stroke Scale; PDGF = Derived growth factor; S100B = S100 calcium-binding protein B; SAP = Serum amyloid P-component; SD = Standard deviation; SDF-1 = Stromal cell-derived factor-1; TIMP-1 = Tissue inhibitor of matrix metalloproteinases-1; TLR = Toll-like receptor; TNFα = Tumor necrosis factor-alpha; TnI = Troponin I; tPA = Tissue plasminogen activator; TSG-1 = Tumor necrosis factor-inducible gene-1; TSP-1 = Thrombospondin-1; VEGF = Vascular endothelial growth factor; W = week(s); WBC = White blood cell; *indicates statistical significant difference.

Supplemental Table 4. Quality Assessment of Each Study Included in the Systematic Review by Using the Modified REMARK Questionnaire

Article	Item of REMARK questionnaire								Percentage of Yes
	1	2	3	4	5	6	7	8	
1	Yes	No	No	Yes	No	Yes	Yes	Yes	62.5
2	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	87.5
3	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	87.5
4	Yes	No	No	Yes	No	Yes	No	Yes	50.0
5	Yes	Yes	Yes	Yes	No	Yes	No	Yes	75.0
6	No	No	Yes	Yes	No	Yes	No	Yes	50.0
7	Yes	No	No	Yes	No	Yes	Yes	Yes	62.5
8	Yes	No	Yes	Yes	No	Yes	No	Yes	62.5
9	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	87.5
10	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	87.5
11	Yes	No	Yes	Yes	No	No	Yes	Yes	62.5
12	Yes	No	No	Yes	No	Yes	Yes	Yes	75.0
13	Yes	No	Yes	Yes	No	Yes	Yes	Yes	75.0
14	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	87.5
15	Yes	No	Yes	Yes	No	Yes	No	Yes	62.5
16	Yes	No	Yes	Yes	No	Yes	No	Yes	62.5
17	Yes	No	Yes	Yes	No	Yes	Yes	Yes	75
18	Yes	No	Yes	Yes	No	Yes	Yes	Yes	75
Percentage of Yes	94.4	33.3	72.2	100.0	5.6	94.4	66.7	100.0	

REMARK = REporting recommendations for tumour MARKer prognostic studies.

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