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Prognostic value of blood interleukin-6 in the prediction of functional outcome after stroke: A systematic review and meta-analysis

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ABSTRACT

We aimed to quantify the association of blood interleukin-6 (IL-6) concentrations with poor outcome after stroke and its added predictive value over clinical information. Meta-analysis of 24 studies confirmed this association with a weighted mean difference of 3.443 (1.592–5.294) pg/mL, despite high heterogeneity and publication bias. Individual participant data including 4112 stroke patients showed standardized IL-6 levels in the 4th quartile were independently associated with poor outcome (OR = 2.346 (1.814–3.033), $p < 0.0001$). However, the additional predictive value of IL-6 was moderate (IDI = 1.5%, NRI = 5.35%). Overall these results indicate an unlikely translation of IL-6 into clinical practice for this purpose.

1. Introduction

Accurately predicting stroke outcome is challenging. Despite the wide number of factors that may influence stroke prognosis, it has been suggested that they could be simplified as the interaction between baseline characteristics of the patient, such as age, gender or stroke severity (Appelros et al., 2003; Saposnik et al., 2008; Wahlgren et al., 2008), and several circumstances that occur after stroke leading to a poor outcome, such as those related to acute therapies (resistance to

Abbreviations: IL-6, interleukin-6; mRS, modified Rankin Scale; BI, Barthel Index; WMD, weighted mean difference; IPD, individual participant data; SD, standard deviation; IQR, interquartile range; OR, odds ratio; CI, confidence interval; ROC, receptor operating characteristic; NRI, net reclassification improvement; IDI, integrated discrimination improvement; NIHSS, National Institutes of Health Stroke Scale; AUC, area under the ROC curve.

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recanalization, reocclusions, hemorrhagic transformation), edema or increased intracranial pressure, or post-stroke infections (Koennecke et al., 2011; Grube et al., 2013). These latter factors represent a unique opportunity for clinicians and researchers to intervene and modify stroke outcome. Even though some blood biomarkers have shown a significant association with neurological deterioration, three-months disability or mortality (Whiteley et al., 2009a), at present there is no biomarker that has proved to be useful for these purposes in the clinical setting, and it is still uncertain whether blood biomarkers add information to simple predictive models based on clinical variables, such as age and severity of stroke (Montaner et al., 2012; Whiteley et al., 2012). Furthermore, a good biomarker should be associated not just with an end point but also with a decision-making process to make easier its translation to clinical practice.

Cerebral ischemia triggers an inflammatory response characterized by the up-regulation of inflammatory cytokines within the brain, as well as in peripheral blood (del Zoppo et al., 2000). Although the over expression of interleukin-6 (IL-6) by astrocytes and microglia may have a dual role in acute ischemia, with both neurotoxic and neuroprotective roles attributed to this cytokine (Van Wagoner and Benveniste, 1999; Muller, 2002), blood levels of IL-6 have been repeatedly associated with poor outcome (Smith et al., 2004; Waje-Andreassen et al., 2005) after stroke. The reason for this association, however, is not fully understood. IL-6 concentration in blood has been correlated with baseline stroke severity, suggesting a plausible role as a biomarker of acute cerebral injury (Orion et al., 2008; Whiteley et al., 2012), but circulating IL-6 may also be related to other factors such as post-stroke infections (Wartenberg et al., 2011). Whether determination of IL-6 adds predictive value to prognostic models of stroke outcome in terms of additional predictive value is also unclear (Orion et al., 2008; Whiteley et al., 2012). Systematic review and meta-analysis of candidate biomarkers has been proposed as an evidence-generating approach (Garcia-Berrocoso et al., 2013a), which may confer a Class II level of evidence for a diagnostic tool (Leone et al., 2013). In this study, our main objective was to evaluate and quantify the association of IL-6 with functional outcome after stroke. Secondary objectives were to explore its added predictive value over clinical information and to assess whether specific causes of poor outcome could underlie this association.

2. Material and methods

2.1. Search

We searched PubMed up to October 2013. A combination of MeSH terms and text words for the terms “stroke”, “IL-6” and “outcome”, using 75 different entry terms, was applied (Supplementary data, S1). Duplicated studies were considered only once. Reference lists of the included articles and reviews that were identified in the search (Laskowitz et al., 1998; Whiteley et al., 2009a; Whiteley et al., 2009b) were hand-searched.

Three authors screened articles considering studies for potential inclusion if they recruited ischemic stroke patients, measured serum or plasma IL-6 concentration during hospitalization and reported long-term (to at least one month) functional outcome with a validated disability scale. Exclusion criteria were language other than English or Spanish; experimental studies with stroke models; reviews or abstracts from conferences, letters, editorials, and case reports; studies reporting outcome just as neurological scores or survival rate; and interventional studies or clinical trials.

2.2. Data extraction and quality assessment

Using a standard template (Supplementary Data, S2), three authors performed the data extraction. Discrepancies were resolved by discussion,

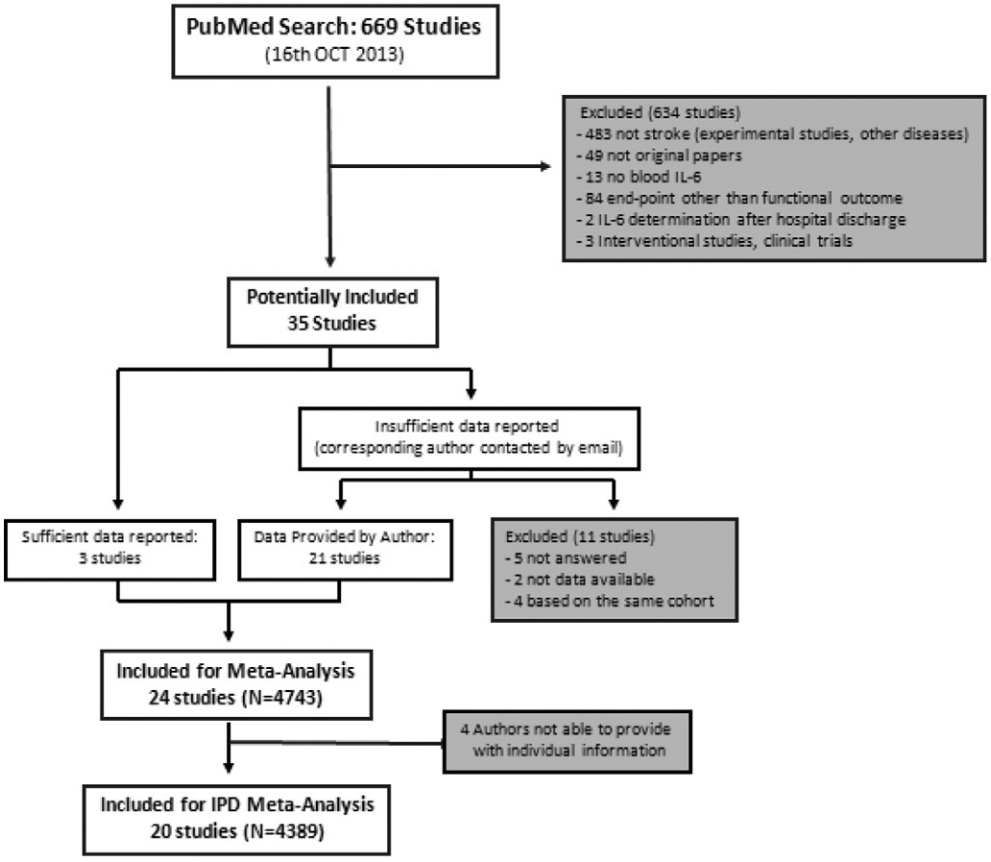

Fig. 1. Flow chart.