Aus der Klinik für Neurologie und klinische Neurophysiologie des
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Schlaganfallschwere und anschließende Lebensqualität – prognostische Marker

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Lino Dominic Braadt

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Inhaltsverzeichnis

Promotionsschrift

Einleitung

Der Schlaganfall stellt weltweit die zweithäufigste Ursache für Tod (11,6% im Jahre 2019) und die dritthäufigste Ursache für den kombinierten Endpunkt Tod und Behinderung (5,7% aller disability-adjusted life-years (DALYs) im Jahre 2019) dar. Weltweit stieg die Anzahl der DALYs zwischen 1990 und 2019 um 32% (1). Hochrechnungen für Europa gehen davon aus, dass die Anzahl der Menschen mit stattgehabtem Schlaganfall zwischen 2017 und 2047 um 27% ansteigen wird (2), insbesondere, da sich das Rezidivrisiko während der letzten 20 Jahre nicht signifikant reduziert hat (3).

Die Prognoseabschätzung ist für den Patienten, aber auch für die Planung der Schlaganfallrehabilitation und Nachsorge, von enormer Bedeutung. Dies ist insbesondere auf Grund der Heterogenität der Schlaganfallpathophysiologie und -ätiologie sowie multipler Einflussfaktoren jedoch nicht trivial.

Häufig erfolgt die Prognoseabschätzung, beispielsweise im Rahmen der Auswahl der Sekundärprophylaxe, mithilfe von Scores wie dem ABCD2 Score oder der National Institute of Health Stroke Scale (NIHSS) (4). Dennoch haben sich bereits Unzulänglichkeiten solcher Reduktionen der biologischen Komplexität auf wenige Faktoren, wie im Falle des ABCD2 Scores, nachweisen lassen (5). Zwar sind Faktoren wie der Diabetes mellitus, der Bluthochdruck und ein Vorhofflimmern bekannte, unabhängige Schlaganfallrisikofaktoren für das Auftreten (6) und das Wiederauftreten von Schlaganfällen (3), es bedarf jedoch noch weiterer Faktoren und Biomarker um die individuelle Prognose zu präzisieren. Wissenschaftlich werden deshalb seit einigen Jahren auch computergestützte Modelle der Bioinformatik, wie Machine learning oder Deep learning, beispielsweise in der Vorhersage einer frühzeitigen neurologischen Verschlechterung (7), des längerfristigen Outcomes (8), oder in der radiologischen Beurteilung von Schlaganfallkern und Penumbra in CT- und MRT-Aufnahmen (9) untersucht. Für die Qualität solcher Algorithmen werden jedoch umfassende und spezifische Daten benötigt (10), was die Notwendigkeit aussagekräftiger, schlaganfallspezifischer Biomarker und Parameter unterstreicht. Blutbiomarker sind hier von besonderem Nutzen, da sie zum einen objektive Indikatoren von physiologischen

und pathologischen Prozessen sind und sich in der Medizin bereits vielfach in der Beurteilung und Vorhersage von Krankheiten bewährt haben (11) und zum anderen als metrische Variablen eine differenziertere Einschätzung erlauben als dichotome Variablen.

Für die weitere Planung bleibt außerdem zu berücksichtigen, dass ein höheres Ausmaß der Behinderung nach einem Schlaganfall mit einer geringeren Lebensqualität korrelieren kann, (12) aber nicht muss (13, 14). Dementsprechend finden sich auch Schwächen der zumeist erhobenen, funktionellen Scores in puncto Lebensqualität: gerade bei relativ gutem funktionellen Outcome besteht häufig ein Mismatch mit der Lebensqualität (15). Aus diesen Gründen sollten sowohl das funktionelle Outcome als auch die Lebensqualität zusammen betrachtet werden. Selbst wenn jedoch etablierte Scores für die Lebensqualität nach Schlaganfall, wie beispielsweise der EQ-5D, verwendet werden, muss berücksichtigt werden, dass auch dieses Scoring nicht allumfassend sein kann und Schwächen aufweist, hier insbesondere bei nicht-motorischen Defiziten (16). Auch hieraus ergibt sich der Bedarf an zusätzlichen aussagekräftigen Markern welche unabhängig von Scores bestehen.

Letztlich sollen beide Publikationen (17, 18) im Rahmen der kumulativen Dissertation einen Beitrag zur verbesserten Outcomeprädiktion bei Schlaganfallpatienten liefern. Während die Identifikation von aussagekräftigen Blutbiomarkern zur Verbesserung spezifischer Vorhersagevariablen beiträgt, erlauben spezifische Patientencharakteristika ein individuelleres Anpassen von Therapie- und Nachsorgeprogrammen.

Diskussion

In der Publikation „Influence of educational status and migration background on the long-term health-related quality of life after stroke" (17) wiesen wir eine signifikante Assoziation zwischen der längerfristigen Lebensqualität nach einem Schlaganfall und dem Bildungshintergrund sowie dem Migrationshintergrund nach.

Dass der sozioökonomische Status, der Bildungshintergrund und das Einkommen, als wichtige prognostische Faktoren für die Überlebensrate nach einem Schlaganfall fungieren können, hat sich bereits belegen lassen (19, 20). Außerdem haben sich bereits verschiedene Faktoren als günstig für die Lebensqualität nach einem Schlaganfall

erwiesen. Hierzu zählen beispielsweise die Wiederaufnahme des Berufs (21) und die Unterstützung durch das soziale Umfeld (22). Als diesbezüglich riskant hingegen haben sich Komorbiditäten wie eine Depression oder Fatigue (23) gezeigt. Auch der Bildungsgrad hat sich bereits in Mittel- bis Niedriglohnländern als unabhängiger Risikofaktor für die Lebensqualität nach dem Schlaganfall belegen lassen (24). In diesem Kontext fügt sich unsere Beobachtung des unabhängigen Risikofaktors niedriger Bildungshintergrund auch in Deutschland schlüssig ein. Dass der Migrationshintergrund in unseren Untersuchungen auch ein unabhängiger Risikofaktor war, deckt sich ebenfalls mit den Ergebnissen einer nicht krankheitsspezifischen Studie, in welcher Personen mit Migrationshintergrund in Deutschland eine schlechtere körperliche gesundheitsabhängige Lebensqualität hatten (25). Im Gegensatz zur bisherigen Literatur publizierten wir erstmals Schlaganfall-spezifische Daten zur Lebensqualität, untersucht mit einem krankheitsspezifischen Fragebogen (SIS (Stroke Impact Scale)) und mit einem langen Beobachtungszeitraum von 12 Monaten. In künftigen Arbeiten könnten angepasste Nachsorgeprogramme erprobt werden und somit der Nutzen einer biographisch angepassten Nachsorge bestätigt werden.

In der Arbeit „Novel inflammatory biomarkers associated with stroke severity: results from a cross-sectional stroke cohort study" (18) untersuchten wir Blutbiomarker und deren Assoziation mit der Schlaganfallschwere. Hier korrelierten die Marker IL6, CKAP4 und CLEC4G positiv und die Marker LY75 und ITGA11 negativ mit der Schlaganfallschwere.

Bezüglich schlaganfallassoziierter Biomarker existierte ebenfalls bereits ein wissenschaftlicher Kontext: so sind beispielsweise C-reaktives Protein (CRP) und IL-6 bekanntermaßen mit schlechterem Schlaganfalloutcome, hierdurch bedingter Behinderung und Überleben assoziiert (26, 27). Auch weiß man, dass IL-6 mit dem Schlaganfallvolumen korreliert und die Bestimmung im Liquor nach dem Schlaganfall entsprechende, prädiktive Aussagekraft besitzt (28). Sowohl IL-6 als auch CKAP4 wurden bereits in Assoziation mit dem NIHSS gebracht (29, 30), IL-6 auch mit dem mRS. Im Falle von CKAP4 wurde anhand von Genclustern die Schlaganfallerkennung untersucht und als signifikant bestätigt. IL-6 hatte sich, wie auch in unseren Ergebnissen, signifikant mit der Schlaganfallschwere korrelieren lassen. Als neue Biomarker in Puncto Schlaganfallschwere konnten wir die Biomarker CLEC4G, LY75 und ITGA11 belegen. Während CLEC4G positiv mit der Schlaganfallschwere korrelierte, war die Korrelation zu LY75 und ITGA11 negativ, sie erwiesen sich also als protektive Marker. Erkenntnisse zu protektiven Markern sind bislang in der Schlaganfall-assoziierten Biomarkerforschung

in der deutlichen Minderheit (11). Da die Schwere eines Schlaganfalls und dessen späteres Outcome jedoch eine Summe aus entstandenem Schaden, Reparationsprozessen und einer individuellen, vorbestehenden Vulnerabilität ist, sind sowohl negative als auch positive Marker notwendige Bestandteile einer umfassenden Betrachtung. Neben den drei erstmals im Schlaganfall-Kontext beschriebenen Biomarkern war unsere Arbeit mit 92 untersuchten Biomarkern in 415 Blutproben, im Vergleich zur bisherigen Literatur, umfangreicher als die meisten Arbeiten (11). Die fehlende Möglichkeit mit dieser Querschnittsstudie einen Kausalzusammenhang herzustellen bietet den ersten Anknüpfungspunkt für künftige longitudinale Studien. Außerdem könnte in einem nächsten Schritt eine Analyse mit den pathophysiologisch unterschiedlichen Schlaganfallätiologien erfolgen.

Wie bereits von Muir et al. diskutiert, sind die Entstehungsmechanismen assoziierter Biomarkererhöhungen oder -reduktionen noch weitestgehend offen: während der Schlaganfall selbst die Ursache sein kann, können auch die ursächlichen Pathomechanismen wie beispielsweise Atherosklerose, oder aber schlaganfallbedingte Komplikationen die Biomarkererhöhung verursachen (26). Aus diesem Grund bleibt die Aussagekraft eines einzelnen Biomarkers diesbezüglich eher unpräzise.

Sinnvoller wird die Bestimmung insbesondere dann, wenn einige aussagekräftige Biomarker kombiniert werden um ein schlaganfallspezifisches Panel zu bilden. Eine andere neurologische Erkrankung, welche bislang ebenfalls einzelner spezifischer Biomarker entbehrt, ist die Multiple Sklerose (MS). Auch hier gibt es bereits eine Vielzahl von signifikanten Biomarkern, wie beispielsweise Neurofilament-Leichtketten (NfL), welche jedoch für sich alleine genommen vielen anderen Einflussfaktoren unterliegen, wie dem Alter oder dem Body-Mass-Index (BMI). Somit diskutieren Yang et al. in ihrer Arbeit eine größere Anzahl an MS-assoziierten Biomarkern und empfehlen zur Steigerung der Aussagekraft eine Panelanalyse mittels Bioinformatik (31).

Auf diese Weise lassen sich letztlich nicht nur die erwähnten Biomarker, sondern auch die biographischen Faktoren zusammenfassen. Deep learning Algorithmen können das Outcome nach einem Schlaganfall prognostizieren (8), eine große Anzahl an Variablen bewältigen und diese selbstständig oder supervidiert analysieren (32). Für die Prognose von Schlaganfallschwere und Lebensqualität nach Schlaganfall besteht somit die Notwendigkeit relevante Daten zu identifizieren, zu erheben und digital auswertbar zu machen.

Zusammenfassung

Die Prognoseabschätzung nach einem Schlaganfall ist sowohl für den Patienten als auch für die Behandler von herausragender Wichtigkeit, insbesondere für die Planung der Rehabilitation und Nachsorge und einer der entscheidenden Faktoren für die langfristige Lebensqualität des Patienten. Die Kenntnis über diesbezügliche Einflussfaktoren ist daher entscheidend um die weitere Nachsorge und Therapieplanung zielgerichteter zu gestalten. Hier ist sowohl die Kenntnis von biographischen Patientendaten, als auch von Blutbiomarkern als zwei wichtige Säulen in der Verbesserung der individuellen Prognoseabschätzung von herausragender Bedeutung.

Der Nachweis des signifikanten Einflusses des Bildungs- und Migrationshintergrundes auf die Lebensqualität nach einem Schlaganfall soll eine Anpassung der Schlaganfalltherapie und insbesondere der -nachsorge an den Patientenbedarf verbessern.

Die positive Assoziation der Biomarker IL-6 und CKAP4 mit der Schlaganfallschwere ließ sich bestätigen, während die positive Assoziation von CLEC4G und die negativen Assoziationen von LY75 und ITGA11 mit der Schlaganfallschwere das bisherige Wissen erweitern.

Alle Daten könnten als aussagekräftige, schlaganfallassoziierte Parameter die Präzision von bioinformatischen Ansätzen unterstützen und verbessern.

Summary

Estimation of patient outcome and prognosis after stroke is of outstanding importance for the patient and for the medical practitioner, especially for planning of rehabilitation and follow-up treatment, as well as for the long-term quality of life of the patient. Therefore, knowledge about influencing factors is mandatory, especially when it comes to modifiable factors. Here, knowing the patients biography is as important as blood biomarkers. Both constitute important parts in improving the individual outcome prognosis.

Proofing the significant influence of educational level and migration background on health-related quality of life after stroke shall improve adaption of stroke care and aftercare to patient.

The positive association between the blood biomarkers IL-6 and CKAP4 with severity of stroke was confirmed, while the positive association of CLEG4G and the negative associations of LY75 and ITGA11 with stroke severity represent novel findings.

All significant and stroke-related data might support and improve the precision of bioinformatical methods.

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ORIGINAL ARTICLE

Influence of educational status and migration background on the long-term health-related quality of life after stroke

Lino Braadt[1] | Christa Meisinger[2] | Jakob Linseisen[2] | Inge Kirchberger[2,3] | Philipp Zickler[1] | Markus Naumann[1] | Michael Ertl[1]

[1]Department of Neurology and Clinical Neurophysiology, University Hospital Augsburg, Augsburg, Germany

[2]Epidemiology, Faculty of Medicine, University of Augsburg, Augsburg, Germany

[3]Institute for Medical Information Processing, Biometry and Epidemiology—IBE, Ludwig-Maximilians-Universität München, Munich, Germany

Correspondence
Michael Ertl, Department of Neurology and Clinical Neurophysiology, University Hospital Augsburg, Augsburg, Germany.
Email: michael.ertl@uk-augsburg.de

Funding information
Augsburg University, Faculty of Medicine

Abstract

Background and purpose: Acute stroke treatment and secondary prevention have tremendously improved functional outcomes after stroke. However, this does not always imply a likewise improvement in health-related quality of life (HRQoL). Knowledge on factors influencing HRQoL after stroke is still scarce, especially regarding social aspects like the level of education and the presence of migration background.

Methods: In the present stroke cohort study, participants were interviewed during their hospital stay and completed a postal questionnaire at 3 and 12 months post stroke. Functional outcomes were assessed by the modified Rankin Scale and HRQoL by evaluating the detailed Stroke Impact Scale (SIS). Logistic regression models were used to determine associations between education, migration background and quality of life end-points.

Results: A total of 945 (mean age 69 years; 56% male) stroke patients were enrolled. After adjusting for confounders, a lower educational level was associated with worse functional outcomes in the SIS domain 'strength' (odds ratio 2.67, 95% confidence interval 1.6–4.4, $p < 0.001$). Migration background was associated with worse outcomes in the SIS domain 'emotion' ($p = 0.007$, odds ratio 1.71, 95% confidence interval 1.2–2.5). Additionally, for female patients worse HRQoL outcomes were found in multiple other SIS domains.

Conclusions: Migration background and a lower educational level were significantly associated with lower long-term HRQoL after stroke. These aspects should be considered in targeted rehabilitation programmes and follow-up support of stroke patients.

KEYWORDS
education, health-related quality of life, migration background, patient-reported outcome measures, stroke

INTRODUCTION

Stroke is a major cause of disability worldwide and accounted for 143 million disability-adjusted life years in 2019 [1]. Over the years, acute stroke treatments, especially intravenous thrombolysis and endovascular therapy, have significantly improved functional outcomes. Stroke outcomes are usually evaluated by the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS). However, functional outcome measures mainly relate to activities of daily life and provide only limited information about the health status from the patient's perspective. Increasing evidence shows that the degree of disability does not necessarily correlate

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with the health-related quality of life (HRQoL) [2]. Thus, stroke outcome research has advanced to additionally include patient-reported outcome measures (PROMs), which also comprise the patient's cognitive and social functions and domains such as symptom burden (e.g., fatigue) or emotional health (e.g., depression) in order to more appropriately reflect HRQoL.

Recently published results from our stroke cohort showed a discrepancy between good functional outcomes and nevertheless significantly reduced HRQoL in the short- and long-term outcome [3]. Factors associated with reduced HRQoL after stroke include depression and fatigue [4], unemployment and an unmarried or unengaged status [5]. Furthermore, a lower educational level showed an association with reduced HRQoL but to date has only been investigated in low- to middle-income countries [6]. It remains unknown whether the educational level is also relevant in high-income countries with different social and occupational situations.

In times of globalization migration is increasing, especially in Western societies. In 2020, 26.7% of the German population had a migration background [7]; in the city of our study (Augsburg) the share of the population with a migration background was even higher at 46.8% in the same year [8]. Different cultural or religious backgrounds influence disease concepts and coping strategies. Nevertheless, the relevance of these factors and their potential impact on HRQoL after stroke is unknown. Therefore, the influence of the education level and migration background on medium- (3 months) and long-term (12 months) outcomes including HRQoL was investigated in a large prospective stroke cohort study.

MATERIALS AND METHODS

Study population, data collection and follow-up

The screening for the enrolment of patients included all adult patients who had been admitted with ischaemic or haemorrhagic strokes as well as transient ischaemic attacks between September 2018 and November 2019 to the University Hospital of Augsburg, Germany. A detailed description of enrolment, methods and conduction of interviews and follow-up data has been published elsewhere [9]. In summary, trained study nurses prospectively recorded all cases with a stroke. After having received written informed consent, a baseline interview and chart review were conducted to assess data on general biographic information, the diagnosis and its details, laboratory findings, treatment and comorbidities. Postal or telephone follow-up examinations were performed after 3 and 12 months, with questions regarding various aspects such as lifestyle, the current level of disability and PROMs using the Stroke Impact Scale (SIS) (see Figure 1).

Outcomes

The patients' functional outcomes were measured using the NIHSS (ranging from 0 to 42) [10] and the mRS [11], which were recorded at admission and at discharge from hospital. Additionally, the mRS was examined by postal follow-up questionnaires. The patient-reported

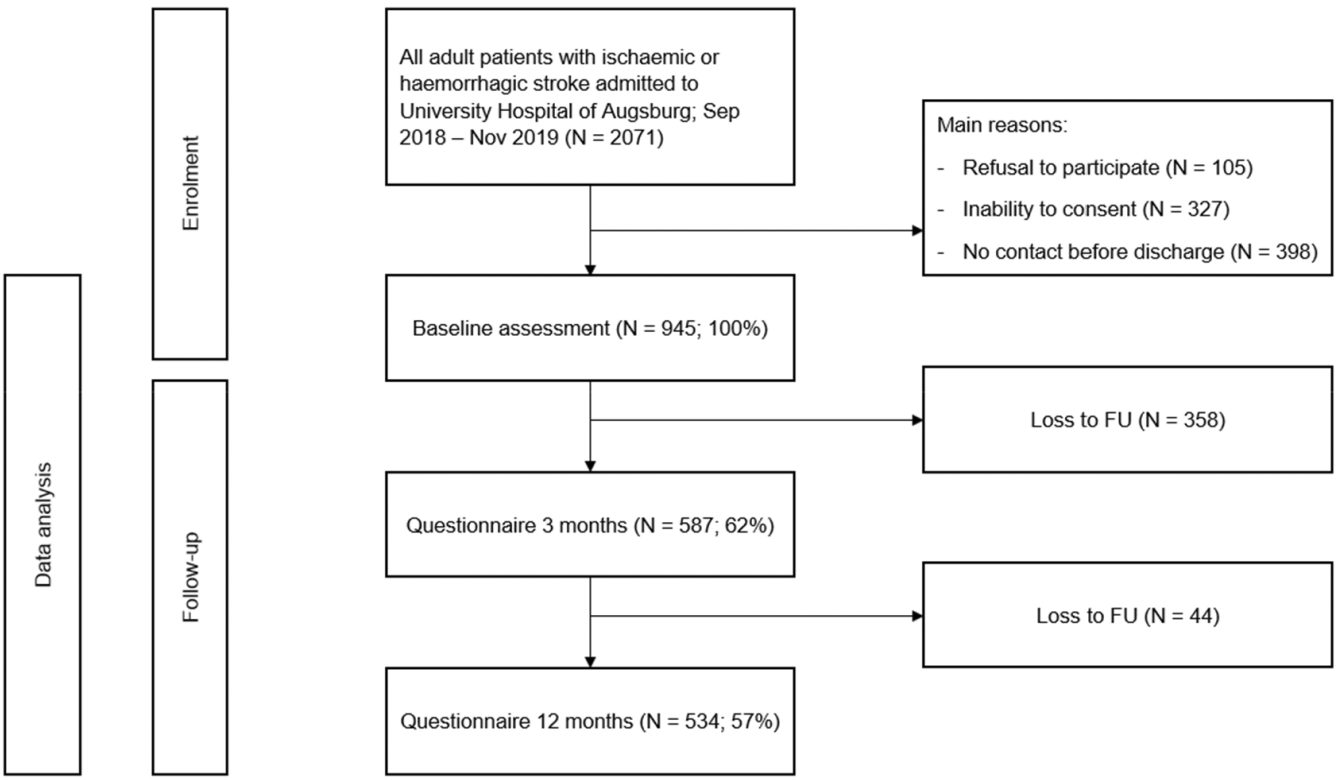

FIGURE 1 Consort chart of patient enrolment and follow-up

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outcome measures were recorded using the SIS [12, 13], which includes 64 items assessed in eight domains and one combined ninth domain. Each domain has a score ranging from 0 to 100 (i.e., from no to full recovery). Namely, the domains refer to strength, hand function, activities of daily life, mobility, a physical domain, memory/thinking, communication, emotion and participation. As an example, the domain emotion evaluates predominant emotions within the past week, whilst the domain strength enquires about the subjective strength of arm, hand, leg and foot. The SIS was assessed after 3 months and again after 12 months.

The validity and reliability of the used scores have been published for the original and the German versions. The interrater reliability (mean kappa) for the NIHSS was 0.80 and for the mRS 0.76 [14]. The instrument reliability of the SIS (Cronbach alpha coefficients) ranged from 0.83 to 0.90 [13].

The educational level was determined using the International Standard Classification of Education (ISCED-97) using six categories. To simplify analysis, the original six ISCED groups were reduced and dichotomized into 'basic education' for those with ISCED levels 1 to 3 and 'higher education' for levels 4 to 6. The approach of grouping ISCED was adapted from other publications [15].

According to the definition of the Federal Statistical Office of Germany a migration background was assumed when either the patient himself/herself or at least one parent was born without German citizenship [16]. For inferential statistical analysis only migration background versus no migration background were differentiated. Respective nationalities were only taken into account for descriptive statistical analysis, and grouping was done whenever complete information on the patient background was available. The groups consist of EU 15 (countries before 2004, including Great Britain), EU 13 (those joined in 2004 and after), the remainder of the European countries but not members of the EU (including Russia), Turkey, the USA and other countries. Those with multiple family antecedents were grouped into 'other'.

Statistical analysis

Baseline characteristics are presented as mean ± standard deviation for normal distributed or median and 25th and 75th quartiles (Q25–Q75) for non-normally distributed continuous variables. Categorized variables are given as numbers (*n*) and percentages (%).

Data were checked for normal distribution using QQ plots, Shapiro–Wilk and Kolmogorov–Smirnoff tests. Medians were compared by Mann–Whitney *U* test, means by *t* test. Categorical data were compared by chi-squared test or Fisher's exact test. For matched-pairs analysis of non-normally distributed variables, Wilcoxon matched-pairs test was used.

Logistic regression analyses were conducted with the domains of SIS as outcome. For this analysis the SIS outcomes were dichotomized into groups above and below the respective median. Independent variables of interest were migration background and basic education.

The models were adjusted for age, sex, body mass index (BMI) and family status. Furthermore, in the models with educational level migration background was also adjusted for, but not vice versa. A p value <0.05 was considered as statistically significant. Statistical analysis was conducted using SPSS software, version 28.0.1.0.

RESULTS

Study population at baseline

Our study included 945 consecutive patients. Their baseline characteristics are shown in Table 1. Women had a worse mRS at admission (2.45 ± 1.52 vs. 2.20 ± 1.48; $p = 0.012$), which did not persist at discharge (1.38 ± 1.46 vs. 1.34 ± 1.41; $p = 0.662$). The NIHSS was not associated with sex, either at admission or at discharge. Regarding basic and higher educational levels there was also a statistically significant difference between mRS at admission (2.34 ± 1.5 vs. 2.08 ± 1.45; $p = 0.045$), which was no longer the case at discharge. Again, the NIHSS in these subgroups did not differ, either at admission or at discharge. Patients with or without migration background did not differ significantly in their mRS at discharge, or NIHSS at both timepoints. For subgroup analyses of grouped migration backgrounds, only one group of patients from EU 13 countries had sufficient statistical power for comparison but showed no differences in functional outcomes such as mRS and NIHSS either at admission or discharge compared to patients without migration background (see Table S1). The educational level was not significantly associated with migration background.

Follow-up after 3 and 12 months

Considering baseline parameters only sex had a significant impact. Women had a worse mRS at admission, but this finding did not persist at all other timepoints including discharge from hospital and the follow-ups at 3 ($p = 0.73$) and 12 months ($p = 0.697$).

Regarding functional outcomes, patients reported a median mRS outcome of 1 both after 3 and after 12 months (median 1 (0–2) vs. 1 (0–2), $p = 0.83$). Almost no changes were observed for all SIS domains between 3 and 12 months (see Table S2). Therefore, further analysis focused on the long-term outcome after 12 months.

A migration background was not associated with significant differences of functional outcomes, either after 3 months ($p = 0.138$) or after 12 months ($p = 0.489$). Patients with a lower educational level had no different functional outcomes after 3 months ($p = 0.509$) but worse outcomes after 12 months ($p = 0.013$).

Men had a significantly better outcome in the domains 'activities of daily life' ($p = 0.001$), 'hand function' ($p < 0.001$), 'mobility' ($p = 0.027$) and in the combined 'physical' domain ($p = 0.025$; see Table S3). Patients without a migration background had a significantly better outcome in the domain 'emotion' compared to those with migrant background ($p = 0.017$; see Table 2). Furthermore,

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TABLE 1 Baseline characteristics given as numbers, mean (±SD) or median (IQR) and numbers (%)

Characteristics	Total study population	Migration background	Basic education
Age (valid)	929	274	602
M; SD	69.3; 13.1	66; 12.8	68.8; 13.3
>80	188 (20)	37 (14)	111 (18)
40–80	719 (77)	228 (83)	475 (79)
<40	22 (2)	9 (3)	16 (3)
Sex (valid)	945	274	602
Female	414 (44)	130 (47)	284 (47)
Male	531 (56)	144 (53)	318 (53)
Stroke type (valid)	945	274	602
Ischaemic stroke	908 (96)	257 (94)	576 (96)
Intracerebral haemorrhage	34 (4)	15 (5)	24 (4)
Subarachnoid haemorrhage	3 (<1)	2 (<1)	2 (<1)
Stroke aetiology (valid)	873	245	552
Macroangiopathy	223 (26)	60 (24)	153 (28)
Microangiopathy	163 (19)	52 (21)	105 (19)
Cardiogenic	219 (25)	50 (20)	140 (25)
Cryptogenic	247 (28)	78 (32)	144 (26)
Other	21 (2)	5 (2)	10 (2)
NIHSS (valid)			
At admission	928; 2 (0–3)	265; 2 (0–3)	590; 2 (0–4)
At discharge	834; 0 (0–4)	245; 0 (0–2)	530; 0 (0–2)
mRS (valid)			
At admission	931; M 2.31 (1.5)	266; M 2.28 (1.47)	591; M 2.34 (1.5)
At discharge	930; M 1.36 (1.43)	269; M 1.25 (1.37)	592; M 1.34 (1.4)
ISCED (valid)	785	274	602
Primary	5 (<1)	4 (1)	5 (<1)
Lower secondary	87 (11)	43 (16)	87 (14)
Upper secondary	510 (65)	164 (60)	510 (85)
Post-secondary, non-tertiary	47 (6)	22 (8)	0
First stage of tertiary	136 (17)	41 (15)	0
Second stage of tertiary	0	0	0
Migration background (valid)	783		600
No migration background	509 (65)		389 (65)
Migration background	274 (35)		211 (35)
Migration background grouped (valid)		255	
EU (before 2004, including Great Britain)		33 (13)	
Remainder EU (after 2004)		79 (31)	
Europe (non-EU, including Russia)		22 (9)	
Turkey		12 (5)	
USA		3 (1)	
Other		106 (42)	

Abbreviations: IQR, interquartile range; ISCED, International Standard Classification of Education; M, mean; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

higher educated patients had better outcomes in the domains 'hand function' ($p = 0.041$), 'participation' ($p = 0.036$), 'strength' ($p < 0.001$), 'mobility' ($p = 0.02$) and in the combined 'physical' domain ($p = 0.003$; see Table 3) compared to less educated patients. The further subgroup analysis of patients with migration background from EU 13 countries did not show significant differences in any domain.

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TABLE 2 Patient-reported outcomes with and without migration background

	Migration background		No migration background		
SIS domain	*n* (valid)	M (Q1–Q3)	*n* (valid)	M (Q1–Q3)	*p*
ADL	166	93.75 (80.73–100)	329	93.75 (83.33–100)	0.77
Emotion	167	72.22 (61.11–86.11)	332	80.56 (66.67–88.89)	0.017
Memory	164	90.63 (75.78–100)	330	90.63 (81.25–100)	0.32
Hand function	152	90.00 (70.00–100)	291	95.00 (75.00–100)	0.23
Communication	165	96.43 (85.71–100)	329	92.86 (85.71–100)	0.84
Participation	156	83.85 (58.59–100)	321	88.89 (66.67–100)	0.09
Strength	147	75.00 (56.25–87.50)	274	75 (62.50–93.75)	0.20
Mobility	164	92.50 (75.00–100)	332	92.50 (77.50–100)	0.64
Physical	166	89.52 (74.14–96.77)	330	90.91 (78.88–96.77)	0.26

Abbreviations: ADL, activities of daily life; M, mean; Q, quartile; SIS, Stroke Impact Scale.

TABLE 3 SIS outcomes with basic and higher education

	Basic education		Higher education		
SIS domain	*n* (valid)	M (Q1–Q3)	*n* (valid)	M (Q1–Q3)	*p*
ADL	378	93.75 (79.17–100)	118	95.83 (85.42–100)	0.06
Emotion	378	77.78 (63.89–88.89)	122	80.56 (65.97–88.89)	0.62
Memory	378	90.63 (78.13–100)	117	93.75 (81.25–100)	0.10
Hand function	340	90.00 (70.00–100)	104	100 (75.00–100)	0.041
Communication	377	96.43 (85.71–100)	118	96.43 (85.71–100)	0.54
Participation	361	87.50 (61.11–100)	117	94.44 (69.44–100)	0.036
Strength	320	75.00 (56.25–81.25)	101	75.00 (68.75–100)	<0.001
Mobility	377	92.50 (75.00–100)	120	95.00 (84.53–100)	0.02
Physical	379	90.32 (75.00–96.77)	118	93.93 (80.74–99.19)	0.003

Abbreviations: ADL, activities of daily life; M, mean; Q, quartile; SIS, Stroke Impact Scale.

After adjusting for the confounders age, BMI, sex, marital status and migration background by logistic regression analyses a significant association between a lower educational level and the outcome 'strength' in the SIS domain persisted (odds ratio 2.67, 95% confidence interval 1.6–4.4, $p < 0.001$). Migration background was significantly related to the domain 'emotion' (odds ratio 1.71, 95% confidence interval 1.2–2.5, $p = 0.007$; see Figure 2).

DISCUSSION

In the present study a significant correlation between the patients' educational status, migration background and HRQoL after stroke was found.

The educational level of patients in the present study was an independent predictive factor for functional outcome and quality of life. It was associated with a worse mRS at admission and after 12 months, an observation that was also found in another stroke patient collective [17]. A low socioeconomic status, which is associated with a low educational level [18], is known to increase the cardiovascular risk and incidence of cardiovascular diseases [19]. In the present study a lower educational level had a significant impact on multiple SIS domains and a negative impact on HRQoL. Similar results have been described in heart failure patients where HRQoL was diminished with lower educational levels. These patients had increased needs of care but less social support [20]. Nevertheless, after consideration of confounding variables like sex, age, BMI, marital status and migration background only the SIS domain 'strength' remained significantly reduced. Since this domain captures the subjective function of the extremities it needs to be considered that a correlation with more severe functional deficits is possible. This assumption is further supported by a worse mRS score at admission in this subgroup. As it is known that stroke severity does not necessarily define HRQoL [3], it can be hypothesized that physical inabilities might impact quality of life even more in patients with a lower educational level.

In the present cohort, a migration background was present in 35% of patients. Of those, a background out of EU 13 was the largest group (31%). Although a link between migration background and lower educational levels is reported [21], this connection was found to be non-significant in our study. Correspondingly, patients with a migration background showed different results from those with lower educational levels. There was no association of migration background with different functional outcomes, either at baseline or at follow-up. Nevertheless, it had a significant impact on HRQoL with negative effects on the SIS domain 'emotion'. This domain

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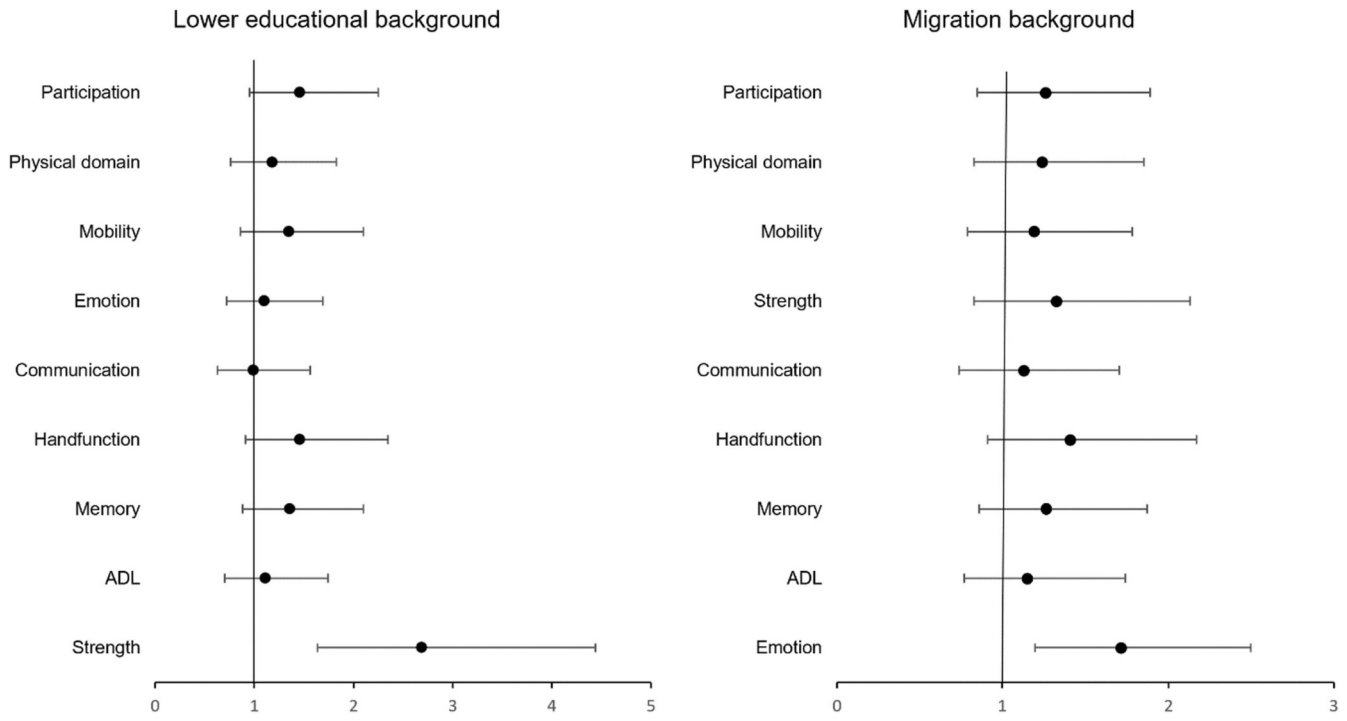

FIGURE 2 Odds ratio, SIS domains in their relation to the educational and migration background. SIS, Stroke Impact Scale

reflects the emotional stability and patient-inherent abilities to cope with a disease. A potential explanation could be that migrants less often use rehabilitation offers [22], which can be associated with lower information availability due to language barriers and with concerns that cultural differences might not be fully understood [23]. As language skills were not enquired about, this aspect could not be investigated in the present study population. In other healthcare issues cultural differences and ethnicity have already been shown to be associated with different disease coping strategies, perception of stress and the use of family support [24, 25]. The dichotomization into an existing or non-existing migration background oversimplifies a complex mixture of different countries and cultural backgrounds also in the present cohort. Our attempt to further subgroup migration backgrounds did not yield significant results due to small subgroup numbers or because the predominant background from EU 13 countries was not the subgroup that caused the significant results. Another important aspect are potential differences between the first or second migration generation relating to the degree of social integration and language competence.

Sex is a decisive factor influencing stroke severity, functional outcome and quality of life after stroke. This could also partly be reproduced in the present cohort, with women having lower mRS values at the timepoint of admission. This effect was restricted to the mRS with NIHSS values not being statistically different. Although the effect was statistically significant, the average difference of 2.45 versus 2.2 points was quite low and the question of clinical significance remains. Although women had more functional impairments and reported worse outcomes in multiple SIS domains both in the present study and in the literature [26, 27], this factor was not associated with the influence of education and migration background on HRQoL after stroke in the present analysis.

Disease-modifying programmes in stroke were the aim of intensive research during the last few years [28, 29]. These programmes are focused on intensive treatment of cardiovascular risk factors to prevent further strokes. The present results underline the need for early screening and identification of additional risk factors like educational level and migration background that have a negative impact on HRQoL. As a consequence, targeted interventions and tailored stroke rehabilitation programmes could be helpful to improve quality of life outcomes. For example, smoking cessation is known to be less successful in low socioeconomic status but can be improved by using an internet-based intervention programme especially directed at this subgroup [30].

Strengths and limitations

The combination of long-term follow-up data in a large prospective stroke cohort, examining PROMs alongside much other detailed information on the patients' biographical and medical data, is a major strength of the study. SIS is a stroke-specific questionnaire, examining various aspects of the individual outcome, allowing analysis of HRQoL in detail. On the other hand, its stroke specificity does not allow a direct comparison with HRQoL measures in other diseases. The overlap of the SIS domain 'strength' with functional outcome measures impedes interpretation. Despite our large cohort, 46% of patients were not included, for example due to refusal to participate (5%) or inability to consent (16%). Of the included patients, 38% were lost to follow-up before 3 months and

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a further 7% of the remaining before 12 months. This represents a potential selection bias, but was partly addressed by checking for stroke severity differences, that is, associations between mRS and NIHSS with migration or educational backgrounds. Since 17% of patients did not provide information about their educational level and their nationality, some statistical effects might not have become significant.

Migration background is a very wide ranging concept with relevant differences in cultural and linguistic aspects. To address these peculiarities, whenever possible the migration backgrounds were grouped into subgroups. Here, backgrounds from EU 15 (EU countries before 2004 [including Great Britain]), EU 13 (those joining in 2004 and after), other European countries without EU membership (including Russia), Turkey, the USA and other countries were differentiated. Patients with multiple antecedents were grouped to 'other background'. By this distinction, the aim was for differentiation between the Western cultures, which would include the example of Austrian descent, eastern European cultures, Arabic countries and others. From these subgroups, only the eastern European group (EU 13) was large enough for statistical analysis. Therefore, more specific influences of particular backgrounds need to be investigated in future studies.

CONCLUSION

In the present study lower educational levels and the presence of a migration background were independent factors significantly associated with a lower long-term HRQoL after stroke. This underlines the importance of investigating quality of life measures in addition to functional outcomes. Our results imply that further improvement in HRQoL could potentially be achieved by tailored rehabilitation programmes and more intense or targeted supportive measures.

AUTHOR CONTRIBUTIONS

Lino Braadt: Formal analysis (lead); investigation (lead); writing – original draft (lead). **Christa Meisinger:** Conceptualization (lead); data curation (equal); formal analysis (supporting); funding acquisition (equal); investigation (equal); methodology (lead); project administration (equal); supervision (equal); validation (equal); writing – review and editing (supporting). **Jakob Linseisen:** Conceptualization (supporting); data curation (equal); funding acquisition (supporting); methodology (lead); project administration (lead); resources (lead); software (lead); supervision (equal); validation (equal); writing – review and editing (equal). **Inge Kirchberger:** Formal analysis (supporting); investigation (equal); methodology (equal); validation (equal); writing – review and editing (equal). **Philipp Zickler:** Conceptualization (equal); methodology (equal); project administration (equal); supervision (equal); writing – review and editing (equal). **Markus Naumann:** Conceptualization (equal); funding acquisition (equal); methodology (equal); project administration (equal); resources (lead); supervision (equal); writing – review and editing (equal). **Michael Ertl:** Conceptualization (lead); formal analysis (equal); funding acquisition (lead); investigation (equal); methodology (equal); project administration (lead); supervision (lead); writing – original draft (lead); writing – review and editing (lead).

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL STATEMENT

The study was approved by the ethics committee of the Ludwig-Maximilians University Munich (29.08.2018, reference number 18-196) in accordance with the ethical standards of the 1964 Declaration of Helsinki. All patients or their legal representatives gave their informed and written consent.

ORCID

Michael Ertl https://orcid.org/0000-0001-5271-4898

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Influence of educational status and migration background on the long-term patient-reported outcome measures (PROM) in stroke

Supplement

Table 1. Comparison of functional outcomes, given as mean (± SD) or median (IQR)

	Group 1[1]	Group 2[2]	*p*-Value
Sex			
mRS			
Admission	**2.45 (1.52)**	**2.2 (1.48)**	**0.012**
Discharge	1.38 (1.46)	1.34 (1.41)	0.662
NIHSS			
Admission	2 (0-5)	2 (0-4)	0.529
Discharge	0 (0-2)	0 (0-2)	0.116
Educational level			
mRS			
Admission	**2.34 (1.5)**	**2.08 (1.45)**	**0.045**
Discharge	1.34 (1.4)	1.28 (1.38)	0.65
NIHSS			
Admission	2 (0-4)	2 (0-4)	0.28
Discharge	0 (0-2)	0 (0-1)	0.23
Migration background			
mRS			
Admission	2.28 (1.47)	2.28 (1.5)	0.961
Discharge	1.25 (1.37)	1.37 (1.41)	0.269
NIHSS			
Admission	2 (0-3)	2 (0-4)	0.33
Discharge	0 (0-2)	0 (0-2)	0.26
EU-13			
mRS			
Admission	2.41 (1.45)	2.29 (1.5)	0.494
Discharge	1.29 (1.35)	1.37 (1.41)	0.662
NIHSS			
Admission	2 (1- 5.75)	2 (0-4)	0.254
Discharge	0 (0-2)	0 (0-2)	0.562

[1] Sex = female, Educational level = basic education, Migration background = present, EU-13 = migration background subgroup; [2] Sex = male, Educational level = higher education, Migration background = none, EU-13 = native patients

Influence of educational status and migration background on the long-term patient-reported outcome measures (PROM) in stroke

Supplement

Table 2. SIS-outcomes after three and twelve months, given as median (IQR)

SIS Domain	3 months	12 months
ADL[1]	93.75 (81.25 - 100)	93.75 (81.25 - 100)
Emotion	77.78 (63.89 - 88.89)	77.78 (63.89 - 88.89)
Memory	90.63 (78.13 - 100)	90.63 (78.13 - 100)
Hand function	95 (75 - 100)	95 (70 - 100)
Communication	96.43 (85.71 - 100)	96.43 (85.71 - 100)
Participation	85.91 (61.11 - 100)	88.89 (62.75 - 100)
Strength	75 (62.5 - 87.5)	75 (62.5 - 87.5)
Mobility	92.5 (78.22 - 100)	92.5 (77.5 - 100)
Physical	90.95 (77.42 - 96.77)	90.63 (77.42 - 96.77)

[1] Activities of daily life

Influence of educational status and migration background on the long-term patient-reported outcome measures (PROM) in stroke

Supplement

Table 3. Patient reported outcomes in females and males

SIS Domain	female		male		
	n (valid)	*M (Q_1 – Q_3)*	*n (valid)*	*M (Q_1 – Q_3)*	*p*
ADL[1]	**218**	**91.67 (77.23 - 97.92)**	**293**	**95.83 (83.71 - 100)**	**0.00**
Emotion	218	77.78 (63.89 - 86.11)	297	77.78 (65.28 - 88.89)	0.63
Memory	214	90.63 (78.13 - 100)	296	93.74 (81.25 - 100)	0.21
Hand function	**186**	**85.00 (65.00 - 100)**	**272**	**95.00 (75.00 - 100)**	**< 0.001**
Communication	218	96.43 (85.71 - 100)	292	96.43 (85.71 - 100)	0.96
Participation	209	84.38 (58.85 - 100)	283	88.89 (66.67 - 100)	0.11
Strength	166	75.00 (56.25 - 87.50)	269	75.00 (62.50 - 93.75)	0.30
Mobility	**220**	**90.00 (75.00 - 100)**	**292**	**95.00 (77.50 - 100)**	**0.03**
Physical	**219**	**88.71 (73.39 - 96.30)**	**293**	**91.94 (78.63 - 97.58)**	**0.03**

[1] - Activities of daily life

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RESEARCH ARTICLE Open Access

Novel inflammatory biomarkers associated with stroke severity: results from a cross-sectional stroke cohort study

Lino Braadt[1*], Markus Naumann[1], Dennis Freuer[2], Timo Schmitz[2], Jakob Linseisen[2†] and Michael Ertl[1†]

Abstract

Background Stroke is a leading cause of mortality and disability worldwide and its occurrence is expected to increase in the future. Blood biomarkers have proven their usefulness in identification and monitoring of the disease. Stroke severity is a major factor for estimation of prognosis and risk of recurrent events, but knowledge on respective blood biomarkers is still scarce. Stroke pathophysiology comprises a multitude of ischemia-induced inflammatory and immune mediated responses. Therefore, the assessment of an immune-related panel in correlation with stroke severity seems promising.

Methods In the present cross-sectional evaluation, a set of 92 blood biomarkers of a standardized immune panel were gathered (median 4.6 days after admission) and related to stroke severity measures, assessed at hospital admission of acute stroke patients. Multivariable logistic regression models were used to determine associations between biomarkers and modified Rankin Scale (mRS), linear regression models were used for associations with National Institute of Health Stroke Scale.

Results 415 patients (mean age 69 years; 41% female) were included for biomarker analysis. C-type lectin domain family 4 member G (CLEC4G; OR = 2.89, 95% CI [1.49; 5.59], $p_{adj} = 0.026$, Cytoskeleton-associated protein 4 (CKAP4; OR = 2.38, 95% CI [1.43; 3.98], $p_{adj} = 0.019$), and Interleukin-6 (IL-6) (IL6; OR = 1.97, 95% CI [1.49; 2.62], $p_{adj} < 0.001$) were positively associated with stroke severity measured by mRS, while Lymphocyte antigen 75 (LY75; OR = 0.37, 95% CI [0.19; 0.73], $p_{adj} = 0.049$) and Integrin alpha-11 (ITGA11 OR = 0.24, 95% CI [0.14, 0.40] $p_{adj} < 0.001$) were inversely associated. When investigating the relationships with the NIHSS, IL-6 ($\beta = 0.23$, 95% CI [0.12, 0.33] $p_{adj} = 0.001$) and ITGA11 ($\beta = -0.60$, 95% CI [−0.83, −0.37] $p_{adj} < 0.001$) were significantly associated.

Conclusions Higher relative concentrations of plasma CLEC4G, CKAP4, and IL-6 were associated with higher stroke severity, whereas LY75 and ITGA11 showed an inverse association. Future research might show a possible use as therapeutic targets and application in individual risk assessments.

Keywords Stroke, Biomarkers, Functional outcome, Stroke severity

Introduction

Stroke is a leading cause of mortality and disability worldwide. Despite recent advancements in acute stroke management, such as thrombolysis and mechanical thrombectomy, the risk of early neurological deterioration remains a substantial risk [1] and long-term outcomes for stroke survivors remain poor. Additionally,

†Jakob Linseisen and Michael Ertl contributed equally to this work.

*Correspondence:
Lino Braadt
lino-dominic.braadt@uk-augsburg.de
[1] Department of Neurology and Clinical Neurophysiology, University Hospital Augsburg, Augsburg, Germany
[2] Epidemiology, Faculty of Medicine, University of Augsburg, Augsburg, Germany

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stroke recurrence rates have not changed over the past 20 years [2].

While scores, such as the ABCD2-score, aim at risk stratification for recurrent events, there is evidence [3] that such few factors do not depict the biological complexity behind the risk of cerebral ischaemia and are therefore pose significant limitations. Outcome prediction is an important part of stroke care in the acute, subacute and chronic phase. It enables planning of rehabilitation goals and offers individualized and also resource-efficient programmes [4].

In the future, artificial intelligence and machine learning-based models are likely to assist physicians estimating the individual patient prognosis. Algorithms, such as the deep neural network, have proven to be effective e.g., in prediction of long-term neurological outcomes [5] or early neurological deterioration [6]. The quality of this technology depends on the number and the specificity of provided variables [7]. Blood biomarkers specifically associated with stroke severity might play an important role in these circumstances.

Several blood biomarkers have been investigated in stroke research, including markers of inflammation, coagulation, oxidative stress, and neuronal injury. Inflammation plays a crucial role in stroke pathophysiology, and several studies have investigated the association between inflammatory biomarkers and stroke outcomes. Elevated levels of inflammatory biomarkers, such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), have been associated with poor stroke outcomes, including increased mortality, disability, and recurrent stroke risk [8–10].

Despite the growing body of evidence on blood biomarkers in stroke, the majority of studies have investigated only a limited number of biomarkers and their association with stroke severity and outcomes. Therefore, there is a need for comprehensive biomarker profiling to identify novel biomarkers and elucidate their role in stroke pathophysiology. Furthermore, by expanding the spectrum of significant biomarkers associated with stroke severity, outcome and risk of recurrence, machine learning methods might gain higher precision in their prediction abilities. As inflammation plays a major role in stroke pathophysiology, we investigated a panel of immune-related blood biomarkers and their association with stroke severity and outcomes in this study.

Material and methods

Study population and data collection

All adult patients admitted with ischemic or hemorrhagic strokes or transient ischemic attacks (TIA) to the University Hospital of Augsburg between September 2018 and November 2019 were screened for inclusion in this stroke cohort. Details of enrolment, methods, conduction of interviews as well as follow-up data have been published elsewhere [11]. In summary, study nurses recorded all stroke cases and excluded those, who refused to consent or were unable to do so. A share of patients was missed before discharge, e.g. because of premature discharge. After having received written informed consent, 44% of all patients were included and baseline interviews and chart reviews were performed. Hereby information about general biography (including age and sex), diagnoses, laboratory findings, treatment, comorbidities and education were gathered as possible confounders. The educational level was dichotomized into "low" and "high" by using International Standard Classification of Education (ISCED)-scores 1–3 and 4–6. This method had already been used elsewhere [12, 13]. Blood was taken, from those patients who gave their consent, during hospital stay and stored serum aliquots were used for the analysis of the "Olink Target 96 Immune Response" panel [14] (see consort chart, Fig. 1). In our analysis we focused on ischemic strokes because of different mechanisms in pathophysiology in comparison to intracerebral bleedings.

Outcome evaluation

Stroke severity was measured using the National Institutes of Health Stroke Scale (NIHSS; ranging from 0 to 42) [15] and the modified Rankin Scale (mRS; ranging from 0 to 6) [16], both were recorded upon hospital admission and discharge. For our present analysis, we focused on the stroke severity at admission, possible acute treatments and individual recovery. The mRS-measures were dichotomized into mRS 0–2 = group 1, 3–5 = group 2. For assessment of protein biomarkers, we used the "Olink Target 96 Immune Response" panel: analyses were carried out by Proximity Extension Assays (PEA) with quantitative polymerase chain reaction (qPCR) readouts [17].

We included only those biomarkers, which were present in at least 25% of patients. Thereby we moved forward to statistical analysis with 63 out of 92 biomarkers.

Inflammatory parameters at admission were measured with C-reactive protein (CRP), measured in mg/dL and leukocyte counts per nL. CRP concentrations of ≥ 0.5 mg/dL and leucocyte counts > 10 leukocytes/nL were regarded as increased.

Statistical analysis

Continuous variables were described by median and the respective interquartile range (IQR), while categorical variables were presented as absolute and relative frequencies. Differences between both mRS groups were

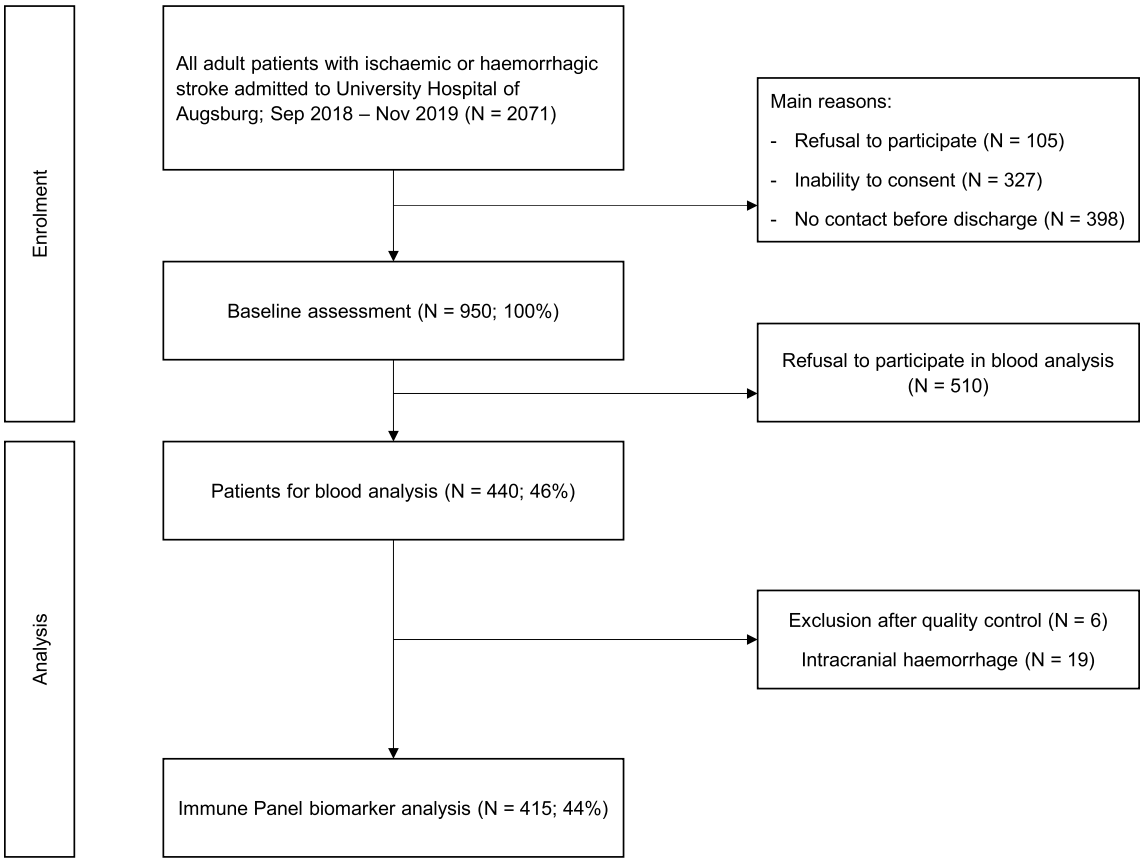

Fig. 1 Consort chart of patient enrolment and analysis

assessed using the Mann–Whitney-U test and Pearson's χ^2-test for continuous and categorical variables, respectively.

To investigate the associations between biomarkers and mRS as proxy for stroke severity we performed multivariable logistic regression models. Associations with NIHSS as severity were investigated performing linear regression models. Due to the assumption of normally distributed residuals, a square root transformation was applied to the NIHSS. Heteroscedasticity was assessed by visual evaluation of the residual plots and by the Breusch-Pagan test.

Possible confounders were selected using a directed acyclic graph (DAG) together with the disjunctive cause criterion. Therefore, all models were adjusted for age, sex, BMI, stroke etiology (macroangiopathic, cardiogenic, microangiopathic, cryptogenic and other etiologies), smoking status (current, ex, never), education level (low, high), sobriety (yes, no), recurrent stroke (yes, no), hypertension (yes, no), alteplase treatment (yes, no), and time between admission and blood collection. To minimize residual confounding, continuous variables were treated as such and the linearity assumption was tested and, if necessary, adapted applying restricted cubic splines. Briefly, in each individual model the variable-specific number of knots between 3 and 5 were compared with regard to Akaike's and Bayesian information criterions (AIC, BIC) and tested against the respective basic model (in which the respective variable were included in a linear way) using the Likelihood ratio test. Finally, we calculated the variance inflation factor (VIF) and assessed the Durbin-Watson statistic to ensure that there was no multicollinearity or autocorrelation.

To exclude patients with relevant clinical infections, possibly due to complications such as pneumonia or urinary tract infection, sensitivity analyses for all associations were performed considering only participants with a CRP ≤ 3 mg/dl.

With regard to multiple testing, p values from regression models were adjusted for the false discovery rate (FDR). All mentioned above analyses were done using the statistical Software R (version 4.2.1).

Correlations between inflammatory parameters (CRP and leukocytes) and biomarkers were investigated using Spearman-correlation. Non-normal distribution was confirmed using QQ-plots and Shapiro–Wilk tests. The latter analyses were done using the statistical software

SPSS (version 28.0.0.0). Statistical tests were performed two-sided at the significance threshold $\alpha = 0.05$.

Results

Baseline characteristics

We included 950 consecutive patients of whom 440 gave their consent for blood sample collection and analysis. From these, six patients were excluded after sample quality control and 19 patients were excluded due to intracranial hemorrhage. A total of 415 samples were sent to the external laboratory of Olink. Baseline characteristics are summarized in Table 1. A total of 412 patients had documented mRS and these were differentiated into two groups of severity, as mentioned above (group 1 n = 221 vs. group 2 n = 190). Age (median 68 (58; 78) vs. 75 (65.5; 80), $p = < 0.001$), sex ($p = 0.014$), depression ($p = 0.019$) and stroke etiology ($p = < 0.001$) differed significantly between the two mRS groups. Furthermore, the days past after admission and blood sample withdrawal differed significantly among both mRS-groups (4.188 (3.08–5.402) vs. 4.888 (3.495–6.593), $p < 0.001$), see Table 2. Regarding specific etiologies, the highest severity was observed in patients with cardiogenic strokes (60 (0.321)) and the least functional impairment was caused by strokes of "cryptogenic and other" stroke etiology (86 (0.415)).

Proteins of the immune panel

For associations between biomarkers and stroke severity, we analyzed mRS and NIHSS separately. After adjustment, results were rated as "not significant", "suggestive significant" (i.e. losing statistical significance after correction) and "significant" after correction for multiple testing by using the FDR approach. The latter was found between mRS and the biomarkers C-type lectin domain family 4 member G (CLEC4G; OR = 2.89, 95% CI [1.49; 5.59], $p_{adj} = 0.026$, Cytoskeleton-associated protein 4 (CKAP4; OR = 2.38, 95% CI [1.43; 3.98], $p_{adj} = 0.019$),, Interleukin-6 (IL6; OR = 1.97, 95% CI [1.49; 2.62], $p_{adj} < 0.001$), Lymphocyte antigen 75 (LY75; OR = 0.37, 95% CI [0.19; 0.73], $p_{adj} = 0.049$) and Integrin alpha-11 (ITGA11; OR = 0.21, 95% CI [0.11; 0.42], $p_{adj} < 0.001$) (see Figs. 2, 3). Regarding the NIHSS, the biomarkers IL6 (β = 0.23, 95% CI [0.12, 0.33] $p_{adj} = 0.001$) and ITGA11 (β = -0.60, 95% CI [-0.83, -0.37] $p_{adj} < 0.001$) were significantly associated on the square root scale as well (see Fig. 4). All results were supported by the sensitivity analyses performed in patients with a CRP $\leq$ 3 mg/dl (see Additional files 1, 2). When correlating all biomarkers with each other, the majority of these showed significant correlations (see Additional file 3).

Table 1 Baseline characteristics of acute stroke patients, given as median (IQR) or absolute and relative frequency

Characteristics	Number of patients	Median (IQR) or n (%)
Age (years)	415	71 (60; 79)
BMI (kg/m^2)	408	26.56 (23.88; 30.06)
NIHSS	411	1 (0; 4)
Fasting status	413	
No		383 (0.927)
Yes		30 (0.073)
Time (days) between admission and blood collection	412	4.625 (3.3; 5.85)
mRS at admission	411	
Group 1 (0–2)		221 (0.538)
Group 2 (3–5)		190 (0.462)
mRS at discharge	410	
Group 1 (0–2)		332 (0.81)
Group 2 (3–5)		78 (0.19)
Sex	415	
Male		243 (0.586)
Female		172 (0.414)
Smoking status	415	
Current		75 (0.181)
Ex-smoker		170 (0.41)
Never		170 (0.41)
Depression	394	
No		360 (0.914)
Yes		34 (0.086)
Educational level	394	
Low		304 (0.772)
High		90 (0.228)
Aetiology	397	
Macroangiopathy		90 (0.227)
Cardiogenic		98 (0.247)
Microangiopathy		76 (0.191)
Cryptogenic and other		133 (0.335)
Recurrent stroke	414	
No		308 (0.744)
Yes		106 (0.256)
Arterial hypertension	415	
No		83 (0.2)
Yes		332 (0.8)
CRP (mg/dL)	406	0.23 (0.11; 0.62)
Leukocytes (/nL)	415	7.81 (6.63; 9.65)

BMI Body mass index, *NIHSS* National Institutes of Health Stroke Scale, *mRS* Modified Rankin Scale, *tmdelta* Days between admission and gathering of sample

Table 2 Comparison patient characteristics by mRS at admission, given as median (IQR) or absolute and relative frequency

Characteristics	n total = 411	mRS 0–2 n = 221	mRS 3–5 n = 190	*p* value
Age	411	68 (58; 78)	75 (65; 80)	**< 0.001**
BMI	404	26.83 (23.84; 29.73)	26.37 (24.2; 30.54)	0.627
NIHSS	411	1 (0; 1)	4 (2; 8)	**< 0.001**
Days between admission and blood taking	408	4.188 (3.08; 5.402)	4.888 (3.495; 6.593)	**< 0.001**
Fasting status	409			0.743
Fasting at admission		203 (0.923)	176 (0.931)	
Not fasting at admission		17 (0.077)	13 (0.069)	
Sex	411			**0.017**
Male		142 (0.643)	100 (0.524)	
Female		79 (0.357)	90 (0.474)	
Smoker	411			0.278
Current		46 (0.208)	28 (0.147)	
Ex-smoker		88 (0.398)	82 (0.432)	
Never		87 (0.394)	80 (0.421)	
Depression	391			**0.019**
No		201 (0.944)	156 (0.876)	
Yes		12 (0.056)	22 (0.124)	
Educational level	391			0.274
Low		160 (0.751)	142 (0.798)	
High		53 (0.249)	36 (0.202)	
Aetiology	393			**< 0.001**
Macroangiopathy		45 (0.217)	44 (0.237)	
Cardiogenic		36 (0.174)	60 (0.323)	
Microangiopathy		40 (0.193)	36 (0.194)	
Cryptogenic and other		86 (0.415)	46 (0.247)	
Recurrent stroke	410			0.595
No		166 (0.755)	139 (0.732)	
Yes		54 (0.245)	51 (0.268)	
Arterial hypertension	411			0.176
No		49 (0.222)	32 (0.168)	
Yes		172 (0.778)	158 (0.832)	

Analysis of continuous variables: Mann–Whitney-U test, Analysis of categorical variables: Pearson's Chi-squared test. *p*-values of < 0.05 are written in bold

BMI Body mass index, *NIHSS* National Institutes of Health Stroke Scale, *mRS* Modified Rankin Scale, *tmdelta* Days between admission and gathering of sample

Correlation with CRP concentration and leukocyte counts

CRP-levels at admission were positively correlated with leukocyte-levels (0.023 mg/dL (0.11–0.62) vs. 7.8/nL (6.63–9.64), $p < 0.001$, $r = 0.277$). Biomarkers, including those which were found to be significantly associated with stroke severity, were also examined for correlation with inflammatory parameters. Here, positive correlations were found for CLEC4G with CRP ($r = 0.227$, $p = < 0.001$) and leukocytes ($r = 0.147$, $p = 0.003$), IL-6 with CRP ($r = 0.375$, $p < 0.001$) and leukocytes ($r = 0.128$, $p = 0.009$), and also with CKAP4 and CRP ($r = 0.24$, $p = < 0.001$). Negative correlations were found between ITGA11 and CRP ($r = -0.308$, $p < 0.001$) and leukocytes ($r = -0.268$, $p < 0.001$). LY75 did not correlate significantly with inflammatory parameters (CRP $p = 0.183$, leukocytes $p = 0.518$). For the remainder of all biomarkers and their correlation with CRP- and leukocyte-levels see Additional file 3.

Furthermore, a significant positive correlation was found between CRP and the mRS ($r = 0.173$, $p < 0.001$), as well as the NIHSS ($r = 0.142$, $p = 0.004$). Leukocytes did not correlate significantly with a functional stroke scale.

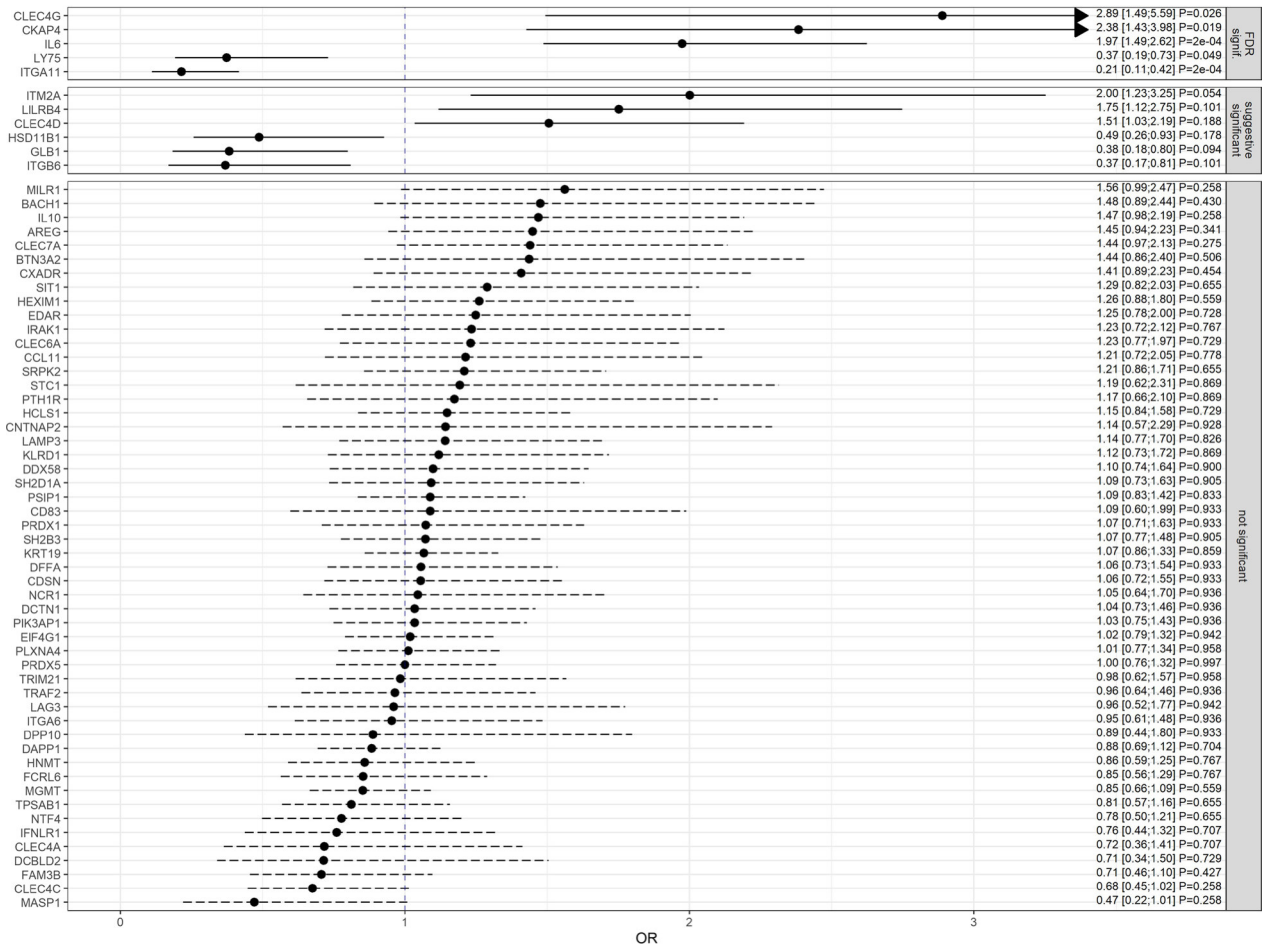

Fig. 2 Odds ratios and 95% confidence intervals for the association between immune biomarkers and mRS (0–2 versus > 2). Presented *p* values are FDR-adjusted. Arrows represent confidence intervals exceeding the plotted x-range

Discussion

The findings of this study confirm the association of certain blood biomarkers with stroke severity and also show new associations. The biomarkers CLEC4G, CKAP4, IL6, LY75 and ITGA11 were found to be significantly associated with stroke severity as measured by mRS and in case of IL6 and ITGA11 also by NIHSS. These results suggest that the levels of these biomarkers may be useful in predicting stroke severity and thus the functional outcome of stroke patients.

Prediction of stroke outcomes requires a high amount of precision, which can be gained by a combination of clinical judgement, validated scales, neuroimaging and laboratory findings. The number of specific blood biomarkers is still low but these markers might play an important role in prognostic scales or even machine-based algorithms, which have already proven to outperform conventional scores in stroke and cardiovascular risk assessment [18–21]. Regarding laboratory findings, reliable and stroke related biomarkers are of special interest in outcome prediction. Among the biomarkers in the present study, we confirmed two positive associations with stroke severity:

First, IL6, a proinflammatory cytokine, was found to be positively associated with both stroke severity as measured by NIHSS and mRS, the latter being a novel finding. One study found that IL6 levels were significantly elevated in the CSF of patients with acute ischemic stroke and were positively correlated with infarct volume and severity [22]. Another study found that IL6 levels were significantly elevated in the serum of patients with acute ischemic stroke and were positively correlated with NIHSS scores [23]. Also, lower IL6 levels at admission were have been associated with complete or near-complete reperfusion after single thrombectomy (first-pass effect) [24]. The authors suggested that IL6 may be a potential biomarker for stroke severity and may serve as a therapeutic target for reducing inflammation and tissue damage following stroke.

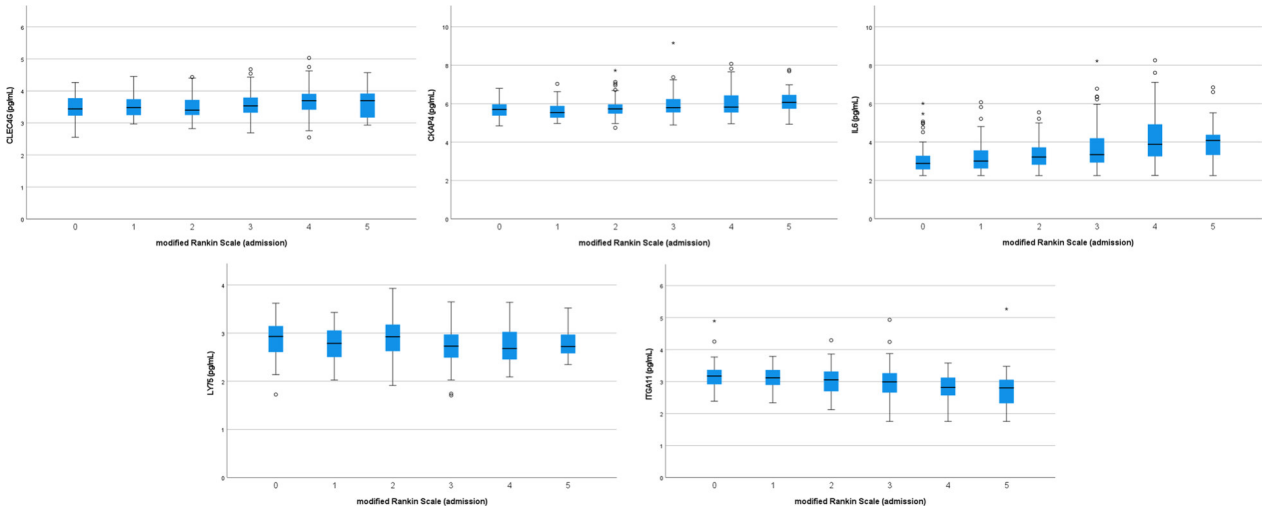

Fig. 3 Relative plasma biomarker concentrations by mRS group (* outliers +/− 3 * IQR)

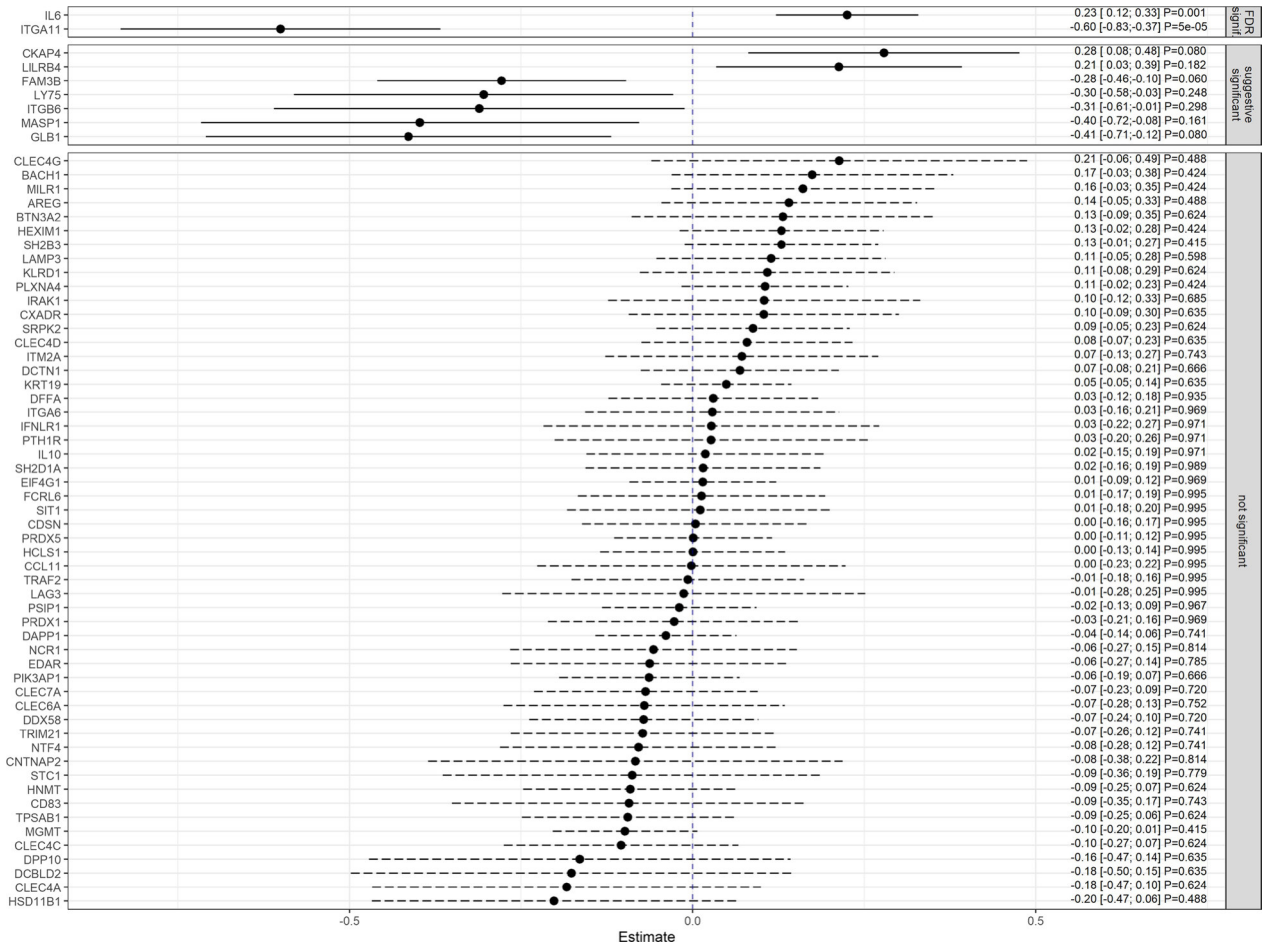

Fig. 4 β estimates and 95% confidence intervals for the association between immune biomarkers and the square root transformed NIHSS. Presented *p* values are FDR-adjusted

The second confirmed association with stroke severity is with CKAP4, although the earlier known associated score was also the NIHSS [25], the mRS represents again a new finding.

CKAP4, a cytoskeleton-associated protein, has been suggested to play a role in the regulation of the immune response and inflammation. One study found that CKAP4 expression was increased in the infarcted area of rat brains after stroke, suggesting that CKAP4 may be involved in the inflammatory response and neuronal damage following stroke [26]. Another study found that CKAP4 was upregulated in peripheral blood mononuclear cells (PBMCs) of patients with acute ischemic stroke [25]. The authors hypothesized that CKAP4 may be involved in the immune response following stroke and may serve as a potential therapeutic target.

To our best knowledge, the following biomarkers have not been correlated with cerebral damage in humans, including ischemia, before. One of these showed also a positive association with stroke severity.

CLEC4G, alternatively known as liver and lymph node sinusoidal endothelial cell C-type lectin (LSECtin), was associated with stroke severity when measured by mRS. It was found to be a regulator of T-cells, acting in hepatic T-cell immune suppression [27]. Furthermore, it is known for acting as a receptor in several viral infections, such as SARS-CoV [28], Japanese encephalitis virus [29], Lassa virus [30] and lymphocytic choriomeningitis virus [31]. All viruses have in common, that they can cause infection of the central nervous system and thus possibly causing structural damage of the brain.

The remaining two biomarkers showed negative associations with stroke severity, indicating their possible protective role in stroke pathophysiology:

LY75, also known as DEC-205, was negatively associated with the mRS. It is an antigen-uptake receptor on dendritic cells [32]. In other studies, LY75 was found to participate in controlling cellular phenotypes in breast cancer and thus their metastatic potential [33]. Regarding environmental factors, DEC-205, together with IL-6 and CD86, was found to be predictive biomarker for respiratory and immune effects of particulate matter [34].

At last, ITGA11 showed a negative association with stroke severity as measured by mRS and NIHSS. ITGA11 belongs to a family of collagen receptors, which have been shown to play a role in fibrosis and tissue repair. A similar integrin molecule (ITGA4) was found to be upregulated in the peri-infarct area of rat brains after stroke and that its inhibition can reduce ischemic brain injury [35]. Therefore, ITGA11 may indeed have a protective role in stroke pathophysiology and may serve as a potential therapeutic target for promoting tissue repair and recovery following stroke.

Strengths and limitations

The analysis of a complete immune panel of biomarkers in a large cross-sectional stroke cohort is a major strength of the present study. Despite the "immune-specificity" of the panel, there are many gaps in knowledge about associations between these biomarkers and central nervous processes, especially stroke.

As limitations, from only 415 out of 950 patients (44%) blood samples were obtained. Many patients who could not be included in the study suffered from potentially more severe strokes (e.g. inability to consent, refusal by caregivers). The time gap between analysis of routine inflammatory parameters (CRP, Leukocytes) and biomarkers is a limitation of the analysis of their correlation. Additionally, the time point for blood sampling for biomarker analysis was not standardized and the delay between the stroke and blood sampling, due to factors such as delayed consent by caregivers, constitutes another limitation of the present study. With a cross-sectional study design, we could not proof a cause-effect-relationship.

Conclusion

The present study confirmed the positive associations between stroke severity and IL6 and CKAP4, but also elucidated novel associations, namely between CLEC4G, LY75 and ITGA11, which enrich the present knowledge of blood biomarkers associated with stroke.

LY75 and ITGA11 were associated with lower stroke severity and might serve as potential therapeutic targets for promoting tissue repair and recovery following stroke.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s42466-023-00259-3.

Additional file 1: Figure S1. Odds ratios and 95% confidence intervals for the association between immune biomarkers and mRS. Presented *p* values are FDR-adjusted. The black-colored estimates represent the results of the main analyses, and the gray-colored ones those of the sensitivity analyses i.e., after exclusion of patients with serum CRP > 3 mg/dl. The left panel shows the associations with a *p* value < 0.05 and the right panel shows the associations with a *p* value ≥ 0.05.

Additional file 2: Figure S2. β estimates and 95% confidence intervals for the association between immune biomarkers and the square root transformed NIHSS. Presented *p* values are FDR-adjusted. The black-colored estimates represent the results of the main analyses, and the gray-colored ones those of the sensitivity analyses i.e., after exclusion of patients with serum CRP > 3 mg/dl. The left panel shows the associations with a *p* value < 0.05 and the right panel shows the associations with a *p* value ≥ 0.05.

Additional file 3: Table S1. Correlations between all immune protein biomarkers, C-reactive protein and leukocytes.

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Author contributions
ME, TS, JL and MN contributed to the study conception and design. Formal analysis was done by DF and LB. The manuscript was drafted by LB and ME. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the ethics committee of the Ludwig-Maximilians University Munich (29.08.2018, Reference number: 18-196) in accordance with the ethical standards laid of 1964 Declaration of Helsinki. All patients or their legal representatives gave their informed and written consent.

Consent for publication
Not applicable.

Competing interests
The authors declared that they have no competing interests.

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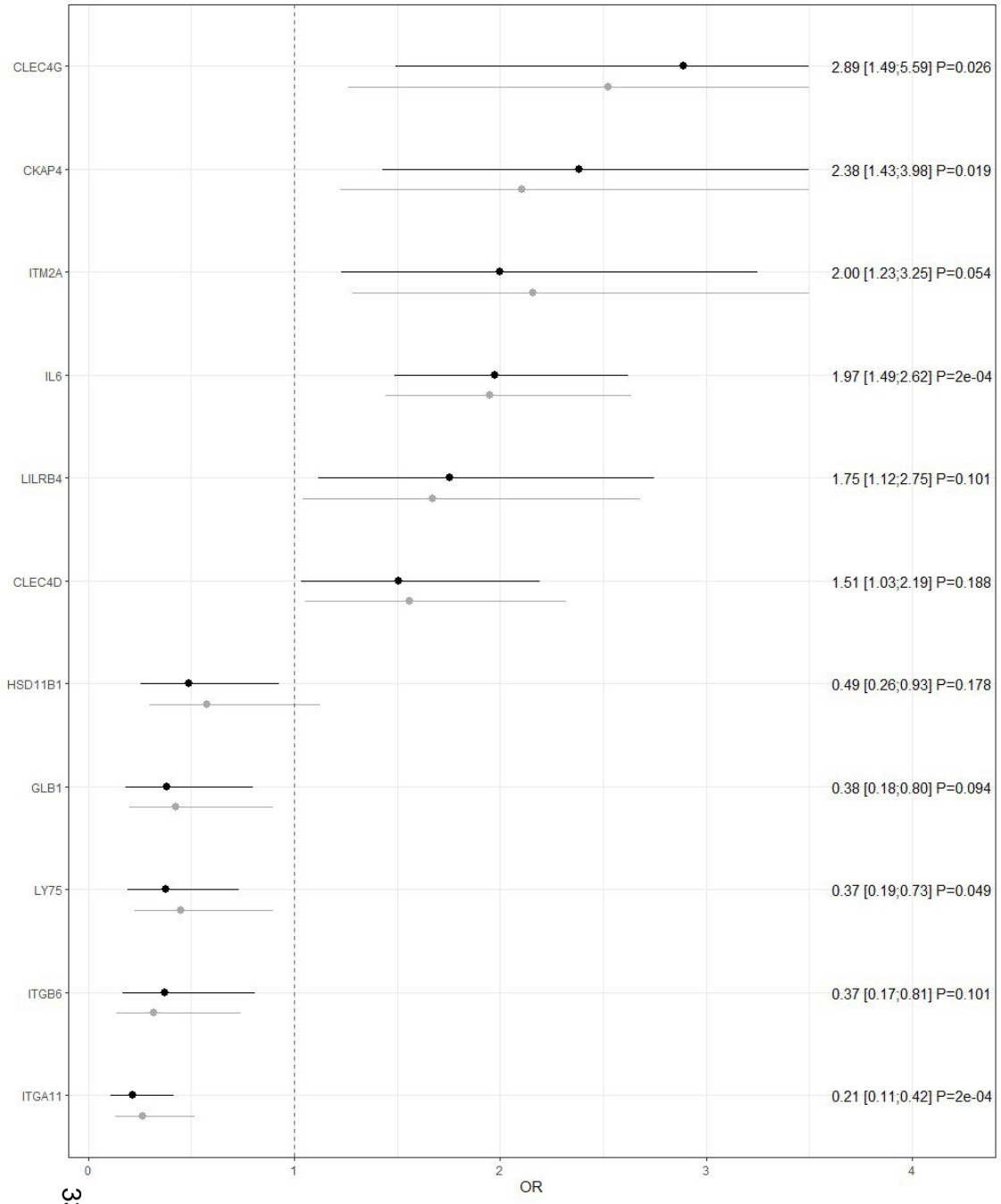
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IL6
LILRB4
CLEC4D
HSD11B1
GLB1
LY75
ITGB6
ITGA11
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2.38 [1.43;3.98] P=0.019
2.00 [1.23;3.25] P=0.054
1.97 [1.49;2.62] P=2e-04
1.75 [1.12;2.75] P=0.101
1.51 [1.03;2.19] P=0.188
0.49 [0.26;0.93] P=0.178
0.38 [0.18;0.80] P=0.094
0.37 [0.19;0.73] P=0.049
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0.21 [0.11;0.42] P=2e-04
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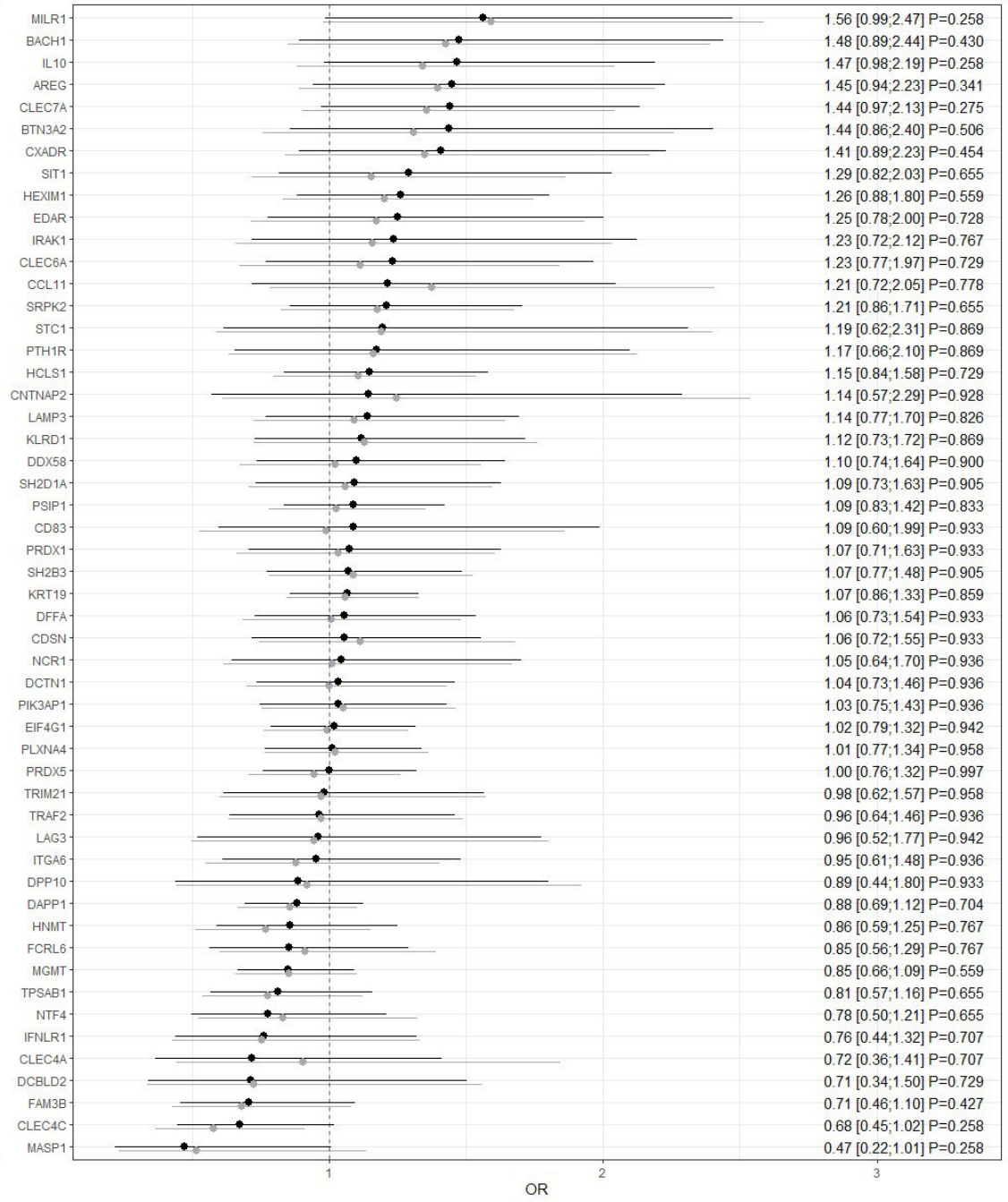
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CCL11
SRPK2
STC1
PTH1R
HCLS1
CNTNAP2
LAMP3
KLRD1
DDX58
SH2D1A
PSIP1
CD83
PRDX1
SH2B3
KRT19
DFFA
CDSN
NCR1
DCTN1
PIK3AP1
EIF4G1
PLXNA4
PRDX5
TRIM21
TRAF2
LAG3
ITGA6
DPP10
DAPP1
HNMT
FCRL6
MGMT
TPSAB1
NTF4
IFNLR1
CLEC4A
DCBLD2
FAM3B
CLEC4C
MASP1
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1.41 [0.89;2.23] P=0.454
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1.26 [0.88;1.80] P=0.559
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1.23 [0.72;2.12] P=0.767
1.23 [0.77;1.97] P=0.729
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1.21 [0.86;1.71] P=0.655
1.19 [0.62;2.31] P=0.869
1.17 [0.66;2.10] P=0.869
1.15 [0.84;1.58] P=0.729
1.14 [0.57;2.29] P=0.928
1.14 [0.77;1.70] P=0.826
1.12 [0.73;1.72] P=0.869
1.10 [0.74;1.64] P=0.900
1.09 [0.73;1.63] P=0.905
1.09 [0.83;1.42] P=0.833
1.09 [0.60;1.99] P=0.933
1.07 [0.71;1.63] P=0.933
1.07 [0.77;1.48] P=0.905
1.07 [0.86;1.33] P=0.859
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1.06 [0.72;1.55] P=0.933
1.05 [0.64;1.70] P=0.936
1.04 [0.73;1.46] P=0.936
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1.02 [0.79;1.32] P=0.942
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0.96 [0.52;1.77] P=0.942
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0.89 [0.44;1.80] P=0.933
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0.86 [0.59;1.25] P=0.767
0.85 [0.56;1.29] P=0.767
0.85 [0.66;1.09] P=0.559
0.81 [0.57;1.16] P=0.655
0.78 [0.50;1.21] P=0.655
0.76 [0.44;1.32] P=0.707
0.72 [0.36;1.41] P=0.707
0.71 [0.34;1.50] P=0.729
0.71 [0.46;1.10] P=0.427
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2
3
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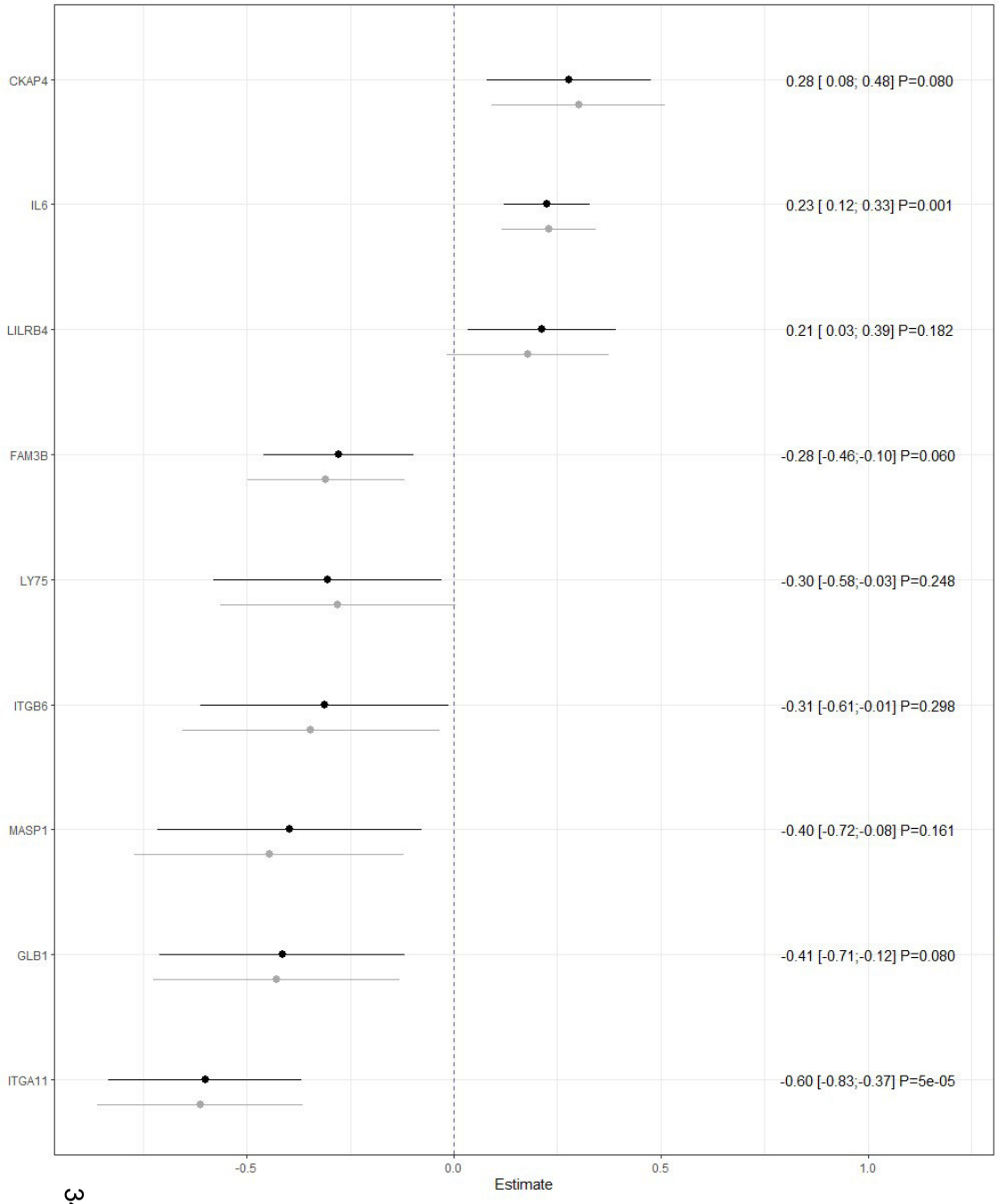
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FAM3B
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LY75
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ITGB6
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GLB1
-0.41 [-0.71;-0.12] P=0.080
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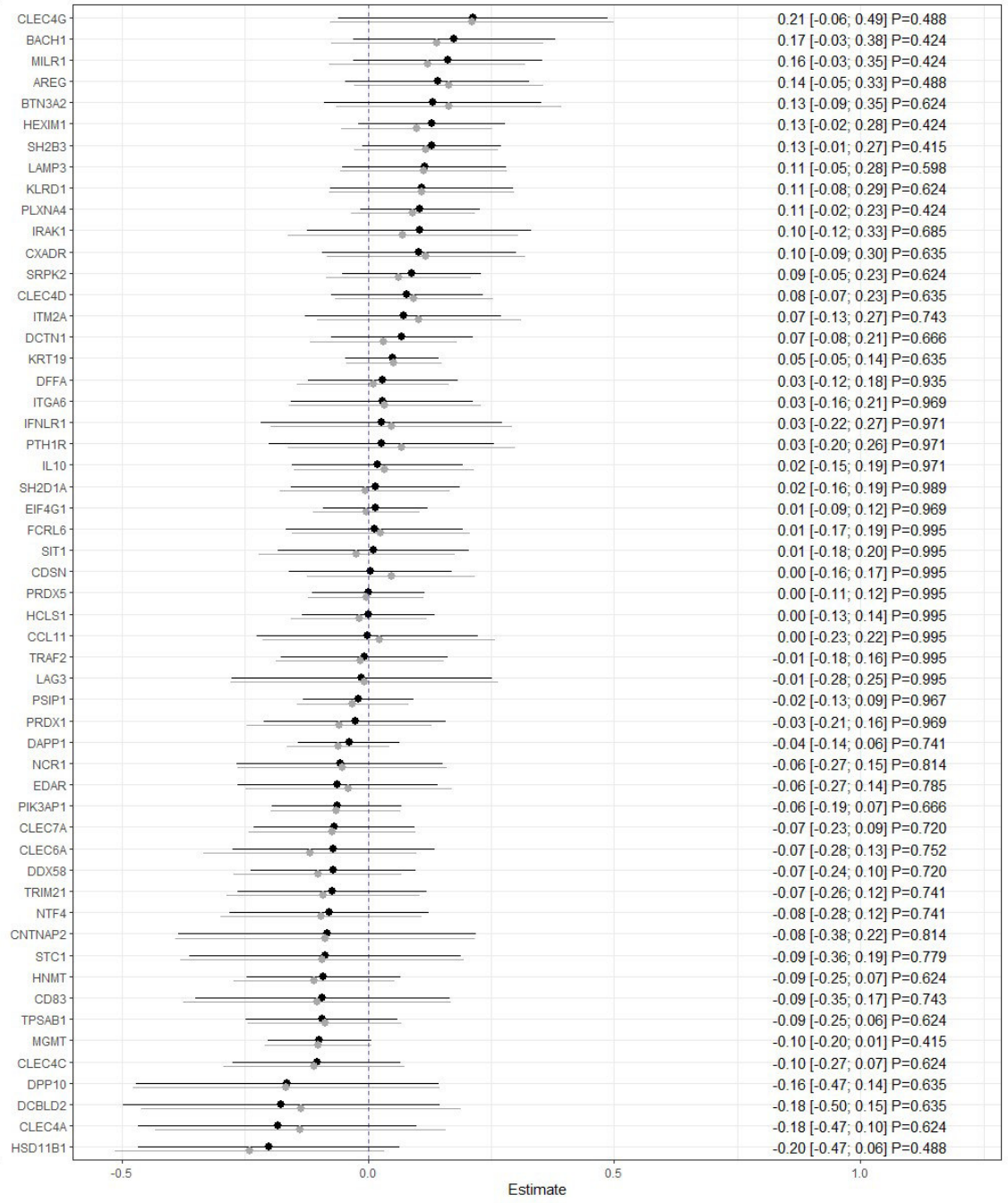
0.5
1.0
Estimate


CLEC4G
0.21 [-0.06; 0.49] P=0.488
BACH1
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MILR1
0.16 [-0.03; 0.35] P=0.424
AREG
0.14 [-0.05; 0.33] P=0.488
BTN3A2
0.13 [-0.09; 0.35] P=0.624
HEXIM1
0.13 [-0.02; 0.28] P=0.424
SH2B3
0.13 [-0.01; 0.27] P=0.415
LAMP3
0.11 [-0.05; 0.28] P=0.598
KLRD1
0.11 [-0.08; 0.29] P=0.624
PLXNA4
0.11 [-0.02; 0.23] P=0.424
IRAK1
0.10 [-0.12; 0.33] P=0.685
CXADR
0.10 [-0.09; 0.30] P=0.635
SRPK2
0.09 [-0.05; 0.23] P=0.624
CLEC4D
0.08 [-0.07; 0.23] P=0.635
ITM2A
0.07 [-0.13; 0.27] P=0.743
DCTN1
0.07 [-0.08; 0.21] P=0.666
KRT19
0.05 [-0.05; 0.14] P=0.635
DFFA
0.03 [-0.12; 0.18] P=0.935
ITGA6
0.03 [-0.16; 0.21] P=0.969
IFNLR1
0.03 [-0.22; 0.27] P=0.971
PTH1R
0.03 [-0.20; 0.26] P=0.971
IL10
0.02 [-0.15; 0.19] P=0.971
SH2D1A
0.02 [-0.16; 0.19] P=0.989
EIF4G1
0.01 [-0.09; 0.12] P=0.969
FCRL6
0.01 [-0.17; 0.19] P=0.995
SIT1
0.01 [-0.18; 0.20] P=0.995
CDSN
0.00 [-0.16; 0.17] P=0.995
PRDX5
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HCLS1
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CCL11
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TRIM21
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NTF4
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CNTNAP2
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STC1
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TPSAB1
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CLEC4C
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-0.18 [-0.47; 0.10] P=0.624
HSD11B1
-0.20 [-0.47; 0.06] P=0.488
-0.5
0.0
0.5
1.0
Estimate

Appendix

Eigenleistung des Doktoranden an den Publikationen

In der Arbeit "Influence of educational status and migration background on the long-term health-related quality of life after stroke" habe ich mich an der Planung und dem Konzept beteiligt, die statistische Auswertung der Daten durchgeführt und das Manuskript geschrieben. Der statistische Teil geschah unter Supervision von Frau Prof. Dr. Meisinger und Herrn Dr. Freuer, die Planung und das Schreiben des Manuskripts erfolgte unter enger Supervision von Herrn PD Dr. Ertl. Bei der Arbeit "Novel inflammatory biomarkers associated with stroke severity: results from a cross-sectional stroke cohort study" habe ich einen Teil der statistischen Auswertung durchgeführt und das Manuskript geschrieben sowie die Revision umgesetzt. Die Regressionsmodelle hierbei wurden von Herrn Dr. Freuer berechnet. Ich habe Korrelationen zwischen den einzelnen Biomarkern untereinander und mit den Entzündungsparametern berechnet. Das Manuskript und die Revision habe ich unter enger Supervision von Herrn PD Dr. Ertl geschrieben. Beide Publikationen wurden unter regelmäßiger Beteiligung und Rückmeldung aller Koautoren angefertigt.

Abkürzungsverzeichnis

DALYs – Disability-adjusted life-years

NIHSS – National Institute of Health Stroke Scale

SIS – Stroke Impact Scale

CRP – C-reaktives Protein

IL-6 – Interleukin-6

CKAP4 – Cytoskeleton-associated protein 4

CLEC4G – C-type lectin domain family 4 member G

LY75 – Lymphocyte antigen 75

ITGA11 – Integrin alpha-11

MS – Multiple Sklerose

NfL – Neurofilament-Leichtketten

BMI – Body-Mass-Index