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ORIGINAL COMMUNICATION

Thrombocytopenia and declines in platelet counts: predictors of mortality and outcome after mechanical thrombectomy

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Abstract

Background and purpose Acute ischemic stroke (AIS) has well-known risk factors. The role of platelets in patients treated using mechanical thrombectomy (MT) has not been studied. The aim of this study was to study if there is an association of initial thrombocytopenia (TP) and a decline of platelets counts (DPC) with the clinical outcomes, mortality and intracranial hemorrhage (ICH) rates in AIS patients treated with MT.

Materials and methods In a case–control study consecutive MT-stroke patients were analyzed. A multivariate logistic regression model was used to test for good clinical outcome (mRS 90 days <= 2) and mortality adjusting for age, initial NIHSS, pretreatment with tPA, statins and platelet inhibitors, occlusion site, time from symptom onset to recanalization, initial TP ($< 150 \times 10^9$/L) and DPC (> 26%). Additionally, rates of ICH were compared.

Results Of 294 patients included, 9.6% had an initial TP and 23.8% a DPC > 26%. The mortality rate in patients with normal platelet counts was 26.1% vs. 48.3% ($p = 0.002$) in patients with initial TP with an aOR of 3.47 (CI 1.28–9.4, $p = 0.005$). No difference regarding the rate of good clinical outcome ($p = 0.204$) and ICH ($p = 0.18$) was observed. A DPC of more than 26% during the first 5 days of hospitalization predicted the rate of mortality (aOR 2.4 CI 1.14–5.04, $p = 0.021$) and the chances of a good clinical outcome (aOR 0.291 CI 0.128–0.666, $p = 0.003$) without significant differences of ICH rates ($p = 0.735$).

Conclusion In AIS patients treated with MT an initial TP was independently associated with higher mortality rates and a marked DPC with higher mortality rates as well as poorer clinical outcomes.

Keywords Acute stroke · Thrombectomy · Thrombocytopenia · Outcomes · Mortality

Introduction

Stroke is a leading cause of mortality and severe neurologic disability. Diverse risk factors for acute ischemic stroke (AIS) have been identified including arterial hypertension, diabetes mellitus, hypercholesterolemia, smoking, ischemic heart disease, atrial fibrillation, previous transient ischemic attack, and previous cerebral infarction [1].

Only few studies analyzed the role of platelets and platelets counts systematically in AIS [2–11]. Without distinction if or which treatment was received, initial thrombocytopenia (TP) is generally considered to be associated with higher mortality rates in AIS patients. Several studies exclusively included AIS patients treated with intravenous (i.v.) thrombolysis, showing that TP does not significantly increase the intracranial hemorrhage (ICH) risk or mortality risk [2, 3, 5, 9]. On the contrary, most recently initial TP was suggested to be associated with increased risk of ICH, but like

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in previous studies, not with an increased risk of mortality [7]. The only study that we are aware of, that further investigated the relevance of a drop in platelet counts (DPC) was published in 1984 by Ramirez-Lassepas et al. reporting that a Heparin-induced DPC in patients with cerebrovascular ischemic disease including partially reversible ischemic neurologic deficits and transient ischemic attacks resulted in poor clinical outcome [12]. DPC has not been studied in AIS patients treated with i.v. thrombolysis.

All these studies mentioned above did not include or did not explicitly mention AIS patients treated with mechanical thrombectomy (MT). Recently large randomized clinical trials demonstrated the superiority of MT for the treatment of large vessel occlusion (LVO) in patients suffering from acute stroke regarding revascularization rates and clinical outcomes compared to sole i.v. thrombolysis [13–17]. MT advanced to the state-of-the-art therapy for AIS caused by LVO.

To the best of our knowledge, Nogueira et al. were the first and only group to have studied mechanical revascularization in AIS patients with abnormal hemostasis (including thrombocytopenia: $n = 6$) on a small ($n = 35$) subgroup of the MERCI/Multi MERCI trial cohorts [18, 19]. They were able to show that abnormal hemostasis did not lead to an increased rate of ICH but decreased rates of good outcome [20]. Since these latter trials, thrombectomy devices and the whole thrombectomy procedure itself have undergone major evolutions and improvements and are thus not easily comparable [21].

Interestingly, in acute coronary syndrome (ACS) and subsequent combined antithrombotic therapy and percutaneous coronary intervention (PCI), TP is a common and well-studied risk factor, which has been associated with increased mortality and increased bleeding risks [22–30]. Recently it has, furthermore, been demonstrated that also an 'acquired' TP and a DPC with normal nadir values are likewise associated with increased mortality and increased bleeding rates [22, 23, 30].

The aim of this study was to investigate the role of TP, acquired TP and DPC in the context of acute ischemic stroke in patients, which have undergone MT regarding incidence, clinical outcome, mortality and the rate of ICH.

Materials and methods

For the present case–control study, we performed a retrospective analysis of a prospectively collected database including all consecutive stroke patients treated by endovascular measures. We identified all consecutive patients treated by endovascular therapy between 01/01/2017 and 31/05/2018. Due to the retrospective study design, written consent was waived by the local ethics committee. Initial TP was defined as platelet counts $< 150 \times 10^9$/L on the day of admission. Acquired TP was defined as platelet counts $< 150 \times 10^9$/L in the following days after MT in a patient which did not have an initial TP.

Intervention

Patients were eligible for endovascular thrombectomy if CT angiography (CTA) confirmed an LVO of the ICA, the middle cerebral artery (MCA) or the basilar artery (BA). Parenchymal infarction was limited to an Alberta Stroke Program Early CT Score (ASPECTS) of > 5 in MCA strokes. No age or perfusion selection was applied within the timeframe of 6 h. Patients beyond the time window of 6 h since symptom onset or with unknown/wake-up symptom onset were selected by a target mismatch on CT Perfusion, calculated by the RAPID software (iSchemaView, Menlo Park, CA, USA) according to recent publications [31, 32]. In BA occlusions no time window was applied. After a femoral access was established a stent-retriever based MT was performed.

Outcome analysis

Technical parameters as well as clinical outcome data were taken from our prospectively collected database. Good clinical outcome was defined as modified Rankin Scale (mRS) 90 days ≤ 2. The mRS at 3 months was either assessed on follow-up visits or by phone call by a mRS-certified study nurse. The platelet counts in the present study were taken from our hospital clinical information system.

Statistical analysis

Baseline, technical and outcome variables between two groups were compared using the Mann–Whitney *U* test, Log rank test, or Fisher's exact test depending on the type of variables analyzed. Receiver operating characteristic (ROC) curve analysis was performed and the maximum Youden index was determined to define the optimal cutoff value for DPC. To adjust for potential confounders, a multivariate logistic regression model was applied to assess the independence of associations. The following prespecified factors were included in a model with either good clinical outcome (mRS 90 days ≤ 2) or mortality as dependent variable: age, initial NIHSS, pretreatment with tPA, pretreatment with statins, pretreatment with platelet inhibitors, occlusion site, time from symptom onset to recanalization, initial TP and DPC > 26%. Results derived from the logistic regression analysis are shown as adjusted odds ratio (aOR) and respective 95% confidence interval (95% CI). Data are generally displayed as n (%) or median, if not indicated otherwise. Statistical significance was assumed at $p < 0.05$.

Written consent was waived by the local ethics committee due to the retrospective design of the present study.

Results

Of the 353 stroke patients treated with MT between 01/01/2017 and 31/05/2018 a total of 294 were included in this study. 59 patients had to be excluded due to lack of follow-up data results, for example if the patient was relocated to another hospital directly after MT ($n=22$) or due to the lack of mRS at 3 months ($n=37$). Of the included patients 50.1% were female with an average age of 75 ± 12.5 years. Detailed information on baseline characteristics and frequency of outcome events are listed in Tables 1 and 2.

All included patients had platelet measurements on the day of admission. Platelet measurements after admission were performed for 260 patients on day 1, 252 patients on day 2, 234 patients on day 3, 200 patients on day 4, and 138 patients on day 5. Patients with more frequent PC-measurements were not more likely to have relevant DPC.

Of the 294 analyzed patients, 9.6% (29/294) showed a TP with a platelet count $< 150 \times 10^9$/L on admission. In the univariate analysis there was no significant difference between patients with a normal or low platelet count regarding sex, age, vessel occlusion, treatment with i.v. rtPA or success in endovascular treatment. There was a statistically significant difference in the rate of preinterventional therapy with statins and platelet inhibitors. Besides that, only the initial NIHSS showed a significant difference between the two groups (14 vs. 17; $p=0.008$). No difference regarding the rate of good clinical outcome defined as a modified Rankin Scale <= 2 (mRS 90d) could be detected between both groups ($p=0.204$) (Fig. 1). Anyhow, there was a significant difference in the mortality rate between these two groups: while the mortality rate 90 days after stroke in patients with normal platelet counts was 26.1% (62/238), patients with initial TP had a mortality rate of 48.3% (14/25) ($p=0.002$). After correcting for potential confounders initial low platelet counts remained an independent predictor of mortality with an aOR of 3.47 (CI 1.28–9.4, $p=0.005$) (Fig. 2). Interestingly, no difference in the rate of hemorrhagic transformations was observed ($p=0.508$). Likewise, after applying the ECASS II criteria there were no statistically significant differences between the two groups ($p=0.18$). The analysis of platelet counts revealed that patients with an initial normal platelet count showed a DPC over the next 2 days of 21 ± 15% of the initial value on average. 94% of the patients (249/265) showed a DPC over the course of the next days. This drop was not detectable in patients with initial TP (Fig. 3). A ROC analysis with calculation of the Youden Index revealed an DPC of more than 26% as the

Table 1 Baseline patient characteristics

	Initial normal platelet count ($n=265$)	Initial thrombocytopenia ($n=29$)	p value	DPC > 26% ($n=84$)	DPC < 26% ($n=210$)	p value
Sex	49.8% female	44.4% female	0.39	34.5% female	57.7% female	< 0.001
Age	74.3 ± 13.1 years	75.5 ± 11 years	0.64	74.8 ± 12.1 years	73.6 ± 13.3 years	0.503
Prior statin treatment	27.3%	20.7%	0.007	27.4%	24.5%	0.193
Prior platelet inhibitor	34.6%	27.6%	0.007	39.3%	29.6%	0.217
Platelet count on admission ($\times 10^9$/L)	246 ± 72	122 ± 26	< 0.001	262 ± 82	224 ± 74	0.001
NIHSS on admission	14 (7–18)	17 (11–22)	0.008	16 (10–20)	13 (7–18)	0.071
Vessel occlusion			0.42			0.381
anterior circulation	79.2%	75.9%		78.3%	74.8%	
posterior circulation	20.8%	24.1%		21.7%	25.2%	
Bridging i.v. rtPA	50.8%	41.4%	0.34	57.1%	44.1%	0.030
Successful recanalization	89.9%	86.2%	0.5	83.7%	90.7%	0.011

Table 2 Outcome data

	Initial normal platelet count ($n=265$) (%)	Initial thrombocytopenia ($n=29$) (%)	p value	DPC > 26% ($n=84$) (%)	DPC < 26% ($n=210$) (%)	p value
mRS < 3	37	24	0.202	21.4	42.3	<0.001
Symptomatic ICH	6.8	10.3	0.180	4.1	6.3	0.230
Mortality	22.6	48.3	0.002	35.7	20.4	0.006

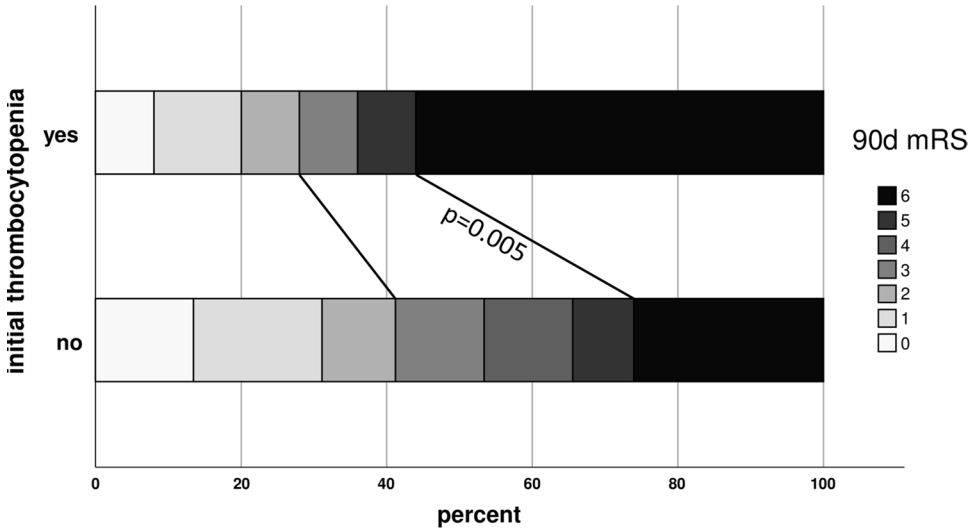

Fig. 1 Clinical outcome of patients with initial TP

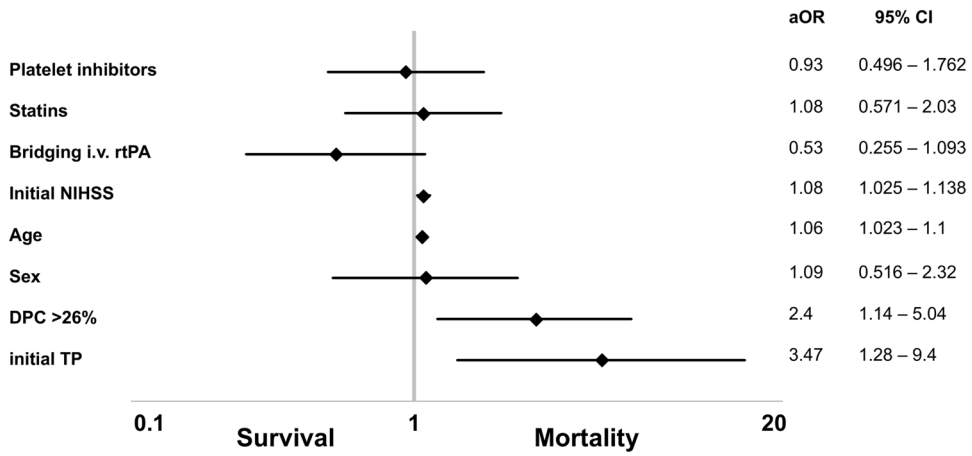

Fig. 2 Mortality rates of patients with initial TP, acquired TP and DPC

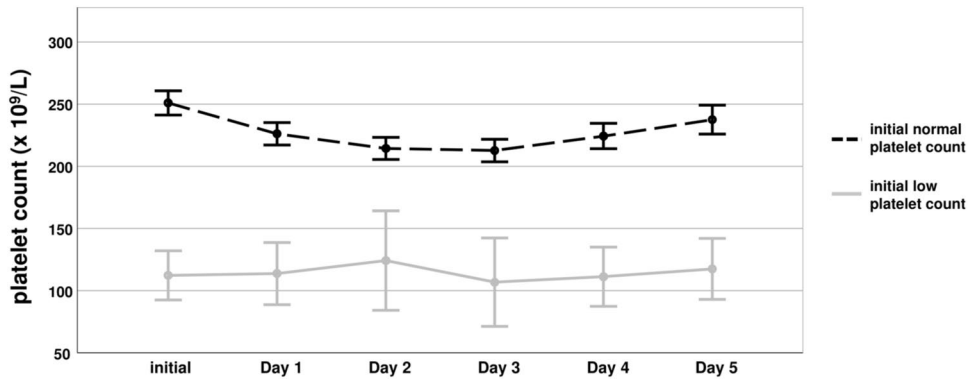

Fig. 3 Time course of platelet counts after endovascular stroke treatment

optimal cut-of value for the prediction of a shift in clinical outcome (sensitivity: 0.811; specificity: 0.553). 28.6% of the patients (84/294) showed a DPC > 26%. Using this cut-off value, a DPC > 26% predicted the rate of mortality (aOR 2.4 CI 1.14–5.04, $p = 0.021$) (Fig. 2) and the chances of a good clinical outcome (aOR 0.291 CI 0.128–0.666, $p = 0.003$) (Fig. 4), after correcting for the prior mentioned prespecified factors in a multivariate regression analysis. Again, no statistically significant difference was detected regarding the rate of ICH between patients with a DPC of either more, or less than 26% ($p = 0.735$). Patients who did not have an initial TP, but showed a TP during the first 5 days of hospitalization were defined as acquired TP. This occurred in 34.3% of cases (101/294). This acquired TP resulted in a trend in lower rate

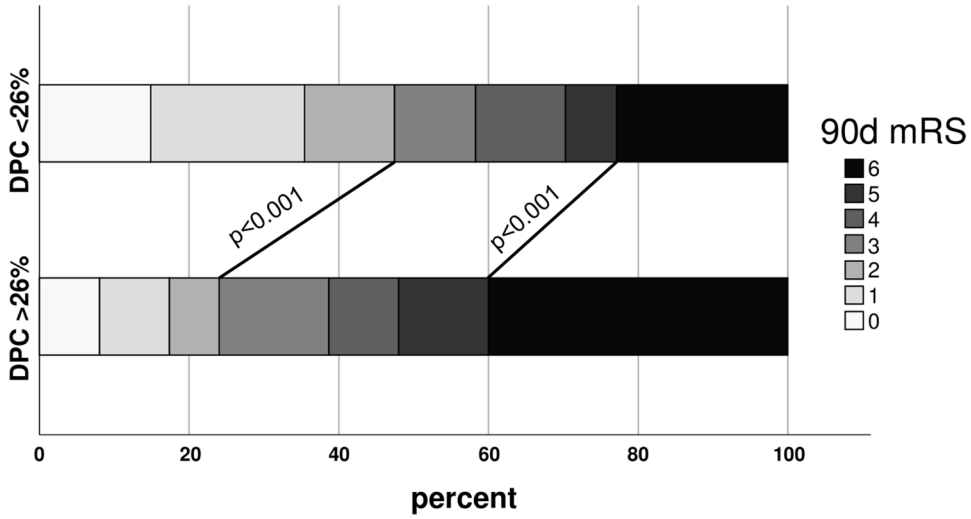

Fig. 4 Clinical outcome of patients with marked DPC

of good clinical outcome (28.7% vs. 36.9%), though missing statistical significance ($p = 0.066$). Again, no statistical significant difference in the rate of ICH could be detected ($p = 0.300$).

Discussion

In this study, we show that the presence of TP on the day of admission and a marked DPC (> 26%) during the first days of hospitalization in an unselected ('real world') group of patients suffering from AIS treated with MT are independently associated with higher mortality rates for TP and higher mortality rates as well as poorer clinical outcomes for DPC, respectively. These findings are in line with similar observations made in patients with acute myocardial infarction/ACS treated with PCI [23, 24, 30, 33].

Similarly to Le Dabriolle et al. [23] we not only focused on absolute platelet counts (initial TP, acquired TP) but also on the procedure-related DPC. The rationale for this was that the extent of DPC may possibly better mirror the MT-related changes in platelet pathophysiology than the absolute platelet nadir measured after the procedure and the following days. Thereby, only patients with substantial drops in platelet counts but in whom the values never reached 'thrombocytopenic' levels were additionally studied.

Since there were no significant differences in ICH for TP or DPC patients, this provides favorable data on the safety of endovascular treatment of acute stroke in such patient collectives.

Like in patients with ACS the causative link between initial TP and marked DPC and increased mortality risk is not entirely clear. TP or DPC related to hemorrhagic complications could have been one plausible explanation. However, as mentioned above the ICH rates were not significantly different compared to the control group in our study. It was further suggested that the presence of TP is associated with female sex or higher age [28]. We corrected for these effects in a multivariate analysis and did not find a significant change. In case of the initial TP cohort, of course comorbidities could be associated with poorer mortality (Supplements Table 1). In case of the DPC cohort, septicemia and disseminated intravascular coagulopathy as further platelet affecting diagnoses were made seldomly (Supplements Table 2).

Trying to decipher the underlying pathophysiology of initial TP and DPC in MT is challenging. One may study patients with immune thrombocytopenic purpura (ITP), an autoimmune hematological condition with decreased production and destruction of platelets due to autoantibodies resulting in thrombocytopenia. The most popular current explanation for an increased thrombogenic risk of these patients and for developing strokes is the presence of platelet microparticles (PMP) [34–40]. Platelets release these microparticles once activated or destructed in vivo, which then provide a membrane surface that is supposed to facilitate the assembly of procoagulant enzyme complexes and thereby predispose to thrombus formation [34, 35, 41]. Interestingly, elevated levels of PMP were not only observed in patients with ITP but also in patients with cerebral ischemic events without underlying ITP [41]. Therefore, PMPs may in general play an important role in hemostasis in patients with TP.

Interestingly, we observed that almost 80% of the patients in the present study displayed a DPC during the first 3 days after MT. To the best of our knowledge this has not been before either. An explanation for this finding could be that thrombocytes have a high turnover during the procedure of MT and, therefore, blood platelet counts drop in the consecutive days. In context of ACS, this was suggested by Karhausen et al. who were able to show an independent association between moderate to severe postoperative TP

after coronary artery bypass grafting surgery [42]. They suggested that DPC may reveal platelet activation and aggregation in a postoperative prothrombotic state. Additionally, in-hospital invasive procedures such as cardiac catheterization and PCI were suggested to cause procedure-related TP due to anticoagulation, hemodilution, or platelet consumption [25, 30]. A recent article investigated the role of VWF, FVIII, ADAMTS13 and inflammatory response in the outcome of acute ischemic stroke MT thoroughly. One finding was that extracted thrombemboli of patients with higher NIHSS in the time of the admission and with worse outcomes contained significantly higher amounts of the inflammatory cells granulocytes, monocytes, vWF/FVIII, fibrin and platelets [43]. Of course to a very limited extent but still noteworthy, this could suggest that platelets are bound to the thrombus and are thus decreased in the peripheral blood.

For conservatively treated patients, Furlan et al. did not find that initial TP had significant higher NIHSS scores on admission [6]. The findings in our study need to be further investigated as they contradict the previous findings showing an association of higher NIHSS scores on admission and initial TP.

Certainly, drugs may influence blood platelet counts. Heparin-induced thrombocytopenia (HIT) is a well-studied phenomenon. In short, administration of heparin leads to an autoantibody-mediated destruction of platelets, also in patients with cerebrovascular ischemic disease [12, 44–46]. In the latter studies, a decrease in platelet counts and a drop of platelets was associated with poor outcome [12]. During the MT procedure in our department all patients received heparin by heparinization of the continuous flush. All patients received between 100 and 500 I.E. of unfractionated heparin during the interventions. Furthermore, the more severe HIT type II usually occurs 5 days after initiation, DPC measured in our study peaked at day two on average. Besides, HIT is rare and remote and only one patient in this study was clinically diagnosed with HIT (Supplements Table 2: Patient ID: 35). We, therefore, believe that it is biologically less plausible that TP and especially the detected DCP are related to heparin.

No patient with initial TP or marked DPC received platelets prior to MT or during hospitalization. At least in the context of ACS it has been elaborated that certain drugs may be linked to TP or DPC besides Heparin: GPIIb/IIIa inhibitors, Abciximab, and thienopyridines [23, 24, 30, 44, 47, 48]. Further investigation of the transferability of these results and drugs in general to AIS patients is necessary, especially since interestingly patients with initial TP had less statins and platelet inhibitors in this study. Anyhow, the use of bridging i.v. rtPA did not affect our results in the multivariate analysis.

Following thrombectomy, microscopic injuries of the endothelial layer could be responsible for platelet activation and platelet consumption. Additionally, changes of the endothelial surface expression caused by ischemia and reperfusion could enhance platelet activation and lead to platelet associated microembolizations of the microcirculation.

In our study cohort the NIHSS of patients with TP on admission was significantly higher (17) compared to patients with normal platelet counts on admission (14) ($p = 0.008$), which may be a bias. For this reason, we corrected for the results above in the multivariate regression analysis.

In this study, the platelet function was not tested, simply due to feasibility reasons. This is certainly a limitation which we are aware of, which, however, we believe not to affect our main findings. Another limitation of this study was the monocentric design. The study design was retrospective with all the inherent limitations, but the data collection were performed prospectively. To rule out possible bias we adjusted the patient base line characteristics using multivariate logistic regression analysis. Nevertheless, unrecognized biasing factors which we were not aware of and which may have an impact on the results can never be totally excluded, e.g. pre-existing medical co-morbidities that could potentially result in abnormal blood platelet counts as well as adversely affect survival after acute ischemic stroke. In addition, the exact cause of death at 90 days after MT could not be thoroughly analyzed, naturally due to the lack of available clinical data. We tried to reduce this limitation by providing data for those patients who deceased during hospitalization. Furthermore, causality between TP and DPC and outcomes cannot be established because unmeasured confounding may be present. The relatively small sample size with only few outcome events increases the risk of chance findings and limited the adjustment for confounding variables. The number of missing data (16.7%) was not small which increased the risk of bias. Following current guidelines, patients were only included if the ASPECT score was > 5; this may also be a potential source for bias.

Summary

In acute ischemic stroke patients after mechanical thrombectomy due to large vessel occlusion thrombocytopenia on the day of admission is independently associated with mortality. Furthermore, a marked decline in platelet counts during the in-hospital management acute ischemic stroke patients after mechanical thrombectomy is independently associated with increased mortality and poorer clinical outcomes. Abnormal platelet counts may, therefore, be used as early available outcome predictors. The underlying pathophysiological background of this effect has to be investigated in further studies.

Compliance with ethical standards

Ethical standards This study was approved by the local ethics committee of the Technical University Munich. It has, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written patient consent was waived by the local ethics committee due to the retrospective design.

Conflicts of interest BF: Consultant for Stryker, speaker honoraria for Medtronic; CM: Consultant for Stryker and Penumbra.

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