INTRODUCTION

The efficacy of endovascular therapy (EVT) in anterior circulation large vessel occlusion acute ischemic stroke has been proven to be beneficial within 24 hours from symptom onset.1-7 The risk of serious adverse events, particularly symptomatic intracerebral hemorrhage is also well known.8 However, these patients are also prone to medical complications and other adverse events.9-11

Abstract

Aim: Endovascular therapy (EVT) in acute stroke is an effective but invasive treatment which is frequently followed by various complications. The aim of the present study was to examine the rate of medical complications and other adverse events following EVT.

Methods: Retrospective single-center study of 380 consecutive stroke patients who received EVT between the years 2015–2019.

Results: A total of 234 (61.6%) patients had at least one recorded medical complication. The most common complication was pneumonia in 154 (40.5%) patients, followed by acute cardiac insufficiency in 134 (35.3%), and myocardial infarction in 22 (5.8%) patients. In multivariate analysis, the need for general anesthesia (OR 3.8 (1.9–7.7)), Charlson Comorbidity Index >3 (OR 1.3 (1.1–1.5)), male gender (1.9 (1.1–1.3)) and high National Institutes of Health Stroke Scale (NIHSS) score at admission (1.1 (1.0–1.2)) were associated with medical complications.

Conclusion: Medical complications are common among unselected stroke patients undergoing EVT. Both comorbidity and stroke severity have an influence on medical complications. Early recognition of complications is essential, because vast majority of patients encountering medical complications have a poor short-term outcome.

KEYWORDS
Strokes, endovascular therapy, complication, outcome
longer hospital length of stay (LOS). However, the frequency of complications and their impact on outcome after EVT for stroke is not well reported. We therefore aimed to evaluate the types, frequency and predictive factors of medical complications and their impact on outcome in patients who underwent endovascular therapy for acute ischemic stroke.

2 | MATERIAL AND METHODS

2.1 | Setting

This single-center retrospective registry study was conducted at Oulu University Hospital, which serves as a Comprehensive Stroke Center for the five northernmost Primary Stroke Centers in Northern Finland. The area consists of 740,000 inhabitants and comprises approximately half of the surface area of Finland. The study was approved by the hospital administration (ref 268/2019) and due to the retrospective study design no statement from the hospital’s ethics committee was needed.

2.2 | Patients and inclusion criteria

All patients who underwent EVT for acute stroke between January 2015 and December 2019 at Oulu University Hospital were retrospectively screened. A total of 380 patients were included into the study.

2.3 | Data extraction

The patients were identified from the Thrombectomy Registry of Oulu University Hospital. Study data were collected by experienced neurologist (first author) using medical records, radiological statements and imaging studies (NearIS Neagen, Finland), laboratory results, anesthesia charts, intensive care unit (ICU) database (Centricity Critical Care Clinisoft, GE Healthcare) and emergency medical service database.

Data describing patients’ baseline characteristics included National Institutes of Health Stroke Scale (NIHSS) score on admission, pre-stroke modified Rankin scale (mRS) score and Charlson Comorbidity Index (CCI). CCI is a scoring method which categorizes patient’s comorbidities based on the diagnoses found in medical records. The gathered intra-procedural variables included treatment with intravenous thrombolysis, the site of arterial occlusion and the type of endovascular technique. The grade of recanalization was defined as modified Thrombolysis in Cerebral Infarction Scale (mTICI). Procedural data included the need for general anesthesia, received amount of contrast media and the time from the stroke onset to groin puncture, from the hospital admission to groin puncture and from the groin puncture to recanalization. Post-procedural variables included NIHSS score on the first post-procedural day, the need for ICU stay and laboratory results and fluid balance during the first three days of the hospital stay. Hospital LOS was calculated and discharge disposition was determined. Functional status at 90 days after EVT was assessed from the medical records. The data were collected on structured forms and digitalized.

2.4 | Complications

The analysis included medical, neurological and puncture site complications during the hospital stay. Medical complications included pneumonia, acute myocardial infarction (AMI), acute kidney injury (AKI), acute cardiac insufficiency, pulmonary embolism (PE), deep venous thrombosis (DVT), delirium, gastrointestinal bleeding and atrial fibrillation. They were categorized as follows. Pneumonia was defined as a condition with infiltrates in chest x-ray with leukocytosis and fever or purulent tracheal secretions. AKI was defined according to KDIGO (Kidney Disease: Improving Global Outcome) criteria which defines AKI as an increase in the serum creatinine by 26.5 µmol/l within 48 hours or an increase to ≥1.5 times baseline. Acute cardiac insufficiency was defined by clinical condition with positive finding in chest x-ray. PE and DVT were defined by clinical condition verified by positive imaging findings. Delirium was defined as a state of confusion, disorientation or reduced awareness when the patient needs recurrent sedative or antipsychotic medication. Gastrointestinal bleeding was defined by clinical condition with positive findings in gastroscopy. Atrial fibrillation was defined with positive ECG findings. Puncture site hematoma or pseudoaneurysm was diagnosed by ultrasound examination, which was performed for all patients having puncture site symptoms. Neurological complications included any hemorrhagic findings in control head computed tomography (CT) and acute seizures.

2.5 | Statistical analysis

Data were analyzed using IBM Statistics for Windows, version 22 (IBM Corp). Categorical variables, presented as absolute numbers and percentages, were compared using Pearson’s chi-squared test. Continuous variables, presented as medians and 25th and 75th percentiles [25th–75th PCT], were analyzed using the non-parametric Mann-Whitney test. P-value less than 0.05 was considered statistically significant. A logistic regression analysis was used to calculate OR and 95% confidence intervals (95% CI) for medical complications. All the variables with univariate significance less than 0.1 were included into model using the enter method. Variables with P-value less than 0.05 and those with significant impact on the log-likelihood function were kept in the model.
RESULTS

A total of 380 thrombectomies were performed during the study period. One patient underwent endovascular procedure twice due to a recurrent stroke during two hospital admissions. The median age of all patients was 70 [60–79] years and 210 (55%) were male. 91% (342/376) of the patients were functionally independent (mRS ≤2) before the stroke onset and 61.6% (234/380) had at least one medical complication.

The most common medical complication was pneumonia in 154 (40.5%) patients followed by acute cardiac insufficiency in 134 (35.3%) patients. Acute myocardial infarction was found in 22 (5.8%) patients and 18 (4.8%) patients had acute kidney injury. Neurological or puncture site complications occurred in 127 (33.4%) patients. Among neurological complications, hemorrhagic findings in control head CT appeared in 80 (21.1%) patients. Puncture site hematoma/pseudoaneurysm appeared in 42 (11.1%) patients. Two of these resulted in retroperitoneal hematomas that were treated conservatively. Two patients needed vascular surgery due to arterial bleeding. (Table 1).

Patients with medical complications were older (74 [63–81] vs 68 [56–74] years, p<0.001) and had more comorbidities (5 [3–7] vs 3 [2–5] CCI score, p<0.001) compared to patients without medical complications. These patients also had more severe neurologic deficit (14 [9–18] vs 13 [7–16] NIHSS score, p=0.006) on hospital admission and higher CRP (4 [0–14] vs 0 [0–6] mg/l, p<0.001) and lower hemoglobin (133 [120–140] vs 139 [127–148] g/l, p=0.001) (Table 2).

Patients who underwent EVT without preceding thrombolysis had more often medical complications than patients treated with bridging therapy (intravenous thrombolysis and EVT) (56.5% vs 43.5%, p=0.008). Successful recanalization (TICI 2b-3) was achieved equally often in both groups (p=0.436). Patients who required general anesthesia had higher rate of complications (35.2% vs 15.1%, p<0.001). (Table 3).

On the first post-procedural day, the patients with medical complications had a higher NIHSS score compared to the patients without medical complications (11 [5–18] vs 5 [3–10], p<0.001). They also had lower hemoglobin (119 [104–130] vs 126 [113–144] g/l, p=0.001), lower albumin (29 [26–32] vs 32 [29–35] g/l, p<0.001) and higher CRP (59 [28–124] vs 20 [10–38] mg/l, p<0.001) levels compared to patients without medical complications. (Table 4).

Patients with medical complications required more often ICU admission (57.3% vs 27.4%, p<0.001) and neurological interventions (9% vs 1.4%, p=0.002) and had a longer hospital LOS (6 [4–9] vs 5 [3–7] days, p<0.001). A total of 41 (10.9%) of all patients were discharged home. Home as discharge disposition was less common in the medical complication group (3.9% vs 22.5%, p<0.001). Functional independence (mRS≤2) at 90 days after hospital discharge was reported in 128 (38.8%) of all patients and was achieved less frequently in the medical complication group (23.4% vs 65.3%, p<0.001). There were 18 (4.8%) in-hospital deaths in the study population and 17 (94.4%) of those were among patients with medical complications. (Table 4).

According to multivariate analysis, OR for medical complications were: need for general anesthesia 3.8 (1.9–7.7), CCI>3 1.3 (1.1–1.5), male gender 1.9 (1.1–3.3), high NIHSS score at admission (11.1 (1.01–1.15), increase in CRP 1.0 (1.0–1.03) and longer time from groin puncture to recanalization (1.01 (1.0–1.02) (Table 5).

DISCUSSION

The main finding of the present study is that medical complications are common after EVT. More than half of the patients had one or more medical complication during the hospital stay. The recorded medical complications were strongly associated with comorbidities and the severity of the stroke. Patients with medical complications had prolonged hospital LOS and deterioration in functional independence at 90 days.

Our finding of medical complications in 61.6% of patients was comparable with a previous study of acute stroke patients treated in a comprehensive stroke unit,13 but their selection of complications was different from ours; they also included general symptoms (pain, fever, falls) as well as progressing stroke in medical complications. A Danish study reported medical complications only in 25% of stroke patients treated in a stroke unit, but they focused on infectious
complications and did not report cardiac problems or kidney injury.\textsuperscript{14} Our finding of a high rate of medical complications might be explained by the age distribution and comorbidities of the medical complication group. Additionally, we described complications in detail and used CCI to determine comorbidities precisely. Furthermore, in our study, 41.6% of the patients were transferred to the hospital from primary stroke centers. Distances in Northern Finland are long and long-lasting transportation exposes critically ill stroke patients to cardiorespiratory and other complications. It is also notable, that part of the recorded complications are not only associated with EVT but also with stroke generally.

In the present study, the most common medical complication was pneumonia followed by cardiac insufficiency. Compared with previous studies, the reported rate of cardiac insufficiency is more pronounced.\textsuperscript{21,22} One explanation for this may be that cardiac insufficiency was previously seldom reported as medical complication after stroke. Acute stroke, especially damage in the insular cortex, which receives blood supply from the middle cerebral artery branches, can result in a variety of cardiac changes due to the dysregulation of autonomic nervous system\textsuperscript{23} and therefore it is obvious that stroke patients are likely to experience various cardiac problems. Moreover, these patients often have traditional risk factors for general atherosclerosis, and may suffer from occult cardiac disease. Accordingly, cardiac problems (cardiac insufficiency and AMI) comprised 41.1% of all medical complications in our study. We reported also atrial fibrillation as a medical complication. Atrial fibrillation might be the underlying etiology for stroke, but likewise ischemic stroke can also trigger various cardiac arrhythmias, including atrial fibrillation, due to brain-heart interaction.\textsuperscript{15} Nevertheless, atrial fibrillation was found only in 10% of EVT patients. Despite consecutive contrast media imaging, AKI was reported only in 4.8% patients in our study, which was similar to the THRACE trial.\textsuperscript{24}

The data regarding medical complications after EVT are scarce or they have been reported as secondary findings since previous studies have focused mainly on the efficacy and benefits of EVT. However, MR CLEAN trial reported also medical complications. The rate of complications in their intervention group was lower compared to ours (pneumonia 10.7% vs 40.5% and cardiac ischemia 0.4% vs 5.8%).\textsuperscript{1}
Our complication rate may be affected by the fact that our patients were older and due to long distances in Northern Finland compared to Netherlands, our time from symptom onset to groin puncture was longer (312 [220–509] vs 260 [210–313] min). Interestingly, we had a similar amount of transfer patients as MR CLEAN trial (41.6% vs 43.8%).

We found the need for general anesthesia an independent risk factor for medical complications. The optimal anesthetic management during EVT is still a matter of controversy and the choice is made on individual basis and according to the local guidelines. This might create a potential bias, as patients who have more severe strokes are often clinically unstable and are therefore likely to have general anesthesia. Concurrently, the same patient group is more likely to have medical complications due to greater stroke burden. Interestingly, sedation without airway protection could be a risk factor for aspiration.

|                         | Patients without medical complications N=146 | Patients with medical complications N=234 | Missing | P-Value |
|-------------------------|---------------------------------------------|-------------------------------------------|---------|---------|
| Treatment with intravenous thrombolysis | IVT + EVT 84 (57.5) 101 (43.5) 0 0.008 | | | |
|                         | EVT alone 62 (42.5) 131 (56.5) 2 | | | |
| Type of stroke onset    | Witnessed 115 (80.4) 185 (79.8) 0.941 | | | |
|                         | Unwitnessed 28 (19.6) 47 (20.2) 5 | | | |
| Occlusion site          | Anterior circulation left 61 (42.7) 89 (38.2) 0.368 | | | |
|                         | Anterior circulation right 59 (41.2) 93 (39.9) 0.368 | | | |
|                         | Posterior circulation 23 (16.1) 51 (21.9) 4 | | | |
| Procedural Details      | DSA only 11 (7.9) 13 (5.6) | | | |
|                         | Aspiration only 47 (33.6) 73 (31.6) | | | |
|                         | Stent retriever 58 (41.4) 120 (51.9) 0.172 | | | |
|                         | Additional Stenting 22 (15.7) 25 (10.8) | | | |
|                         | Technical failure 2 (1.4) 0 (0.0) 9 | | | |
| Recanalization result   | TICI 3 79 (61.7) 120 (58.5) 0.436 | | | |
|                         | TICI 2B−2C 44 (34.4) 70 (34.1) | | | |
|                         | TICI 0−2A 5 (3.9) 15 (7.4) 47 | | | |
| Anesthetic management   | Conscious i.v. sedation 124 (84.9) 151 (64.8) <0.001 | | | |
|                         | General anesthesia 22 (15.1) 82 (35.2) 1 | | | |
| Process measures        | Median time from stroke onset to groin puncture (min) 308 [210–430] 312 [220–509] 9/7 0.497 | | | |
|                         | Median time from hospital admission to groin puncture (min) 69 [44–107] 83 [50–125] 8/8 0.102 | | | |
|                         | Median time from groin puncture to recanalization (min) 42 [26–57] 50 [31–86] 9/9 0.002 | | | |
|                         | Contrast media amount (ml) 170 [135–200] 180 [140–215] 5/3 0.085 | | | |

Note: The modified Thrombolysis in Cerebral Infarction scale ranges from 0 to 3, with a grade of 2b, 2c or 3 indicating successful reperfusion.

Abbreviations: DSA, digital subtraction angiography; EVT, endovascular therapy; IVT, intravenous thrombolysis.
and pneumonia. In this patient group, we were not able to show the relation between pneumonia and EVT under sedation.

C-reactive protein (CRP) is a common marker of acute infection and it also reflects a systemic inflammatory reaction and tissue damage in acute stroke. High CRP has been associated with unfavorable outcome also in patients who did not experience acute infections. Our study reveals that increased CRP is associated with medical complications. This finding might partly be explained by acute infections. However, high CRP has also been linked to generalized atherosclerosis, hypertension, obesity and high level of serum cholesterol. Accordingly, increased CRP also reflects multiple comorbidity and again underlines that these patients are prone to complications and worse outcome. It is essential to recognize the risk groups and when possible, focus on prevention of complications among these patients.

### 4.1 Clinical impact

Previous studies have shown that successful recanalization is an important factor predicting good functional outcome after

| TABLE 4 Clinical, Imaging and Functional Outcomes. |
|-----------------------------------------------|-----------------------------------------------|----------------|----------------|
| Clinical                                      |                                                                                         |
| Median NIHSS score on 1st post-procedural day  | 5 [3–10.5]                                 | 11 [5–18] | 2/12 | <0.001 |
| ICU stay                                      | 40 (27.4)                                  | 134 (57.3) | 0  | <0.001 |
| Acute seizure                                 | 2 (1.4)                                    | 14 (6.0)  | 5  | 0.034  |
| Neurological complication                     | 18 (12.3)                                  | 57 (24.4)  | 0  | 0.004  |
| Imaging                                       |                                                                                         |
| CT HI1-2                                      | 14 (9.6)                                   | 37 (16)   | 0  | 0.08   |
| CT PH1                                        | 4 (2.8)                                    | 11 (4.8)  | 0  | 0.04   |
| CT PH2                                        | 3 (2.1)                                    | 7 (3.0)   | 4  | 0.575  |
| Safety                                        |                                                                                         |
| Puncture site hematoma/pseudoaneurysm         | 15 (10.3)                                  | 27 (11.5) | 0  | 0.702  |
| Neurosurgical intervention                    | 2 (1.4)                                    | 21 (9.0)  | 0  | 0.002  |
| Laboratory Results                             |                                                                                         |
| CRP mg/L                                      | 20 [10.5–38]                               | 59 [27.5–124] | 103/86 | <0.001 |
| Hemoglobin g/L                                | 126 [113-144.5]                            | 119.5 [104-130] | 90/84 | 0.001  |
| Creatinine µmol/L                             | 65 [55–72]                                 | 63 [50.5–79.5] | 95/79 | 0.712  |
| Albumin g/L                                   | 32 [29–35]                                 | 29 [26–32] | 106/109 | <0.001 |
| Fluid balance 1 ml                            | −350 [−800–−50]                            | −337.5 [−1000–90] | 17/60 | 0.989  |
| Fluid balance 2 ml                            | −315 [−875–50]                             | −450 [−1025–−100] | 22/62 | 0.084  |
| Fluid balance 3 ml                            | −200 [−750–50]                             | −400 [−1100–−130] | 51/83 | 0.018  |
| HOSPLOS (d)                                   | 5[3–7]                                     | 6[4–9]    | 2/0 | <0.001 |
| Discharge position                            |                                                                                         |
| Home                                          | 32 (22.5)                                  | 9 (3.9)   | 0  | <0.001 |
| Primary care-rehabilitation                    | 42 (29.6)                                  | 118 (50.9)| 0  |        |
| Secondary care-hospital                        | 67 (47.2)                                  | 88 (37.9) | 6  |        |
| Dead                                          | 1 (0.7)                                    | 17 (7.3)  | 6  |        |
| Functional outcome at 90 days                 |                                                                                         |
| mRS 0–2-Functional independency               | 79 (65.3)                                  | 49 (23.4) | 50  | <0.001 |
| mRS 3–4-Moderate disability                  | 31 (25.6)                                  | 68 (32.5) | 50  | <0.001 |
| mRS 5-Bedridden                               | 5 (4.1)                                    | 33 (15.8) | 50  | <0.001 |
| mRS 6-Dead                                    | 6 (5.0)                                    | 59 (28.2) | 50  | <0.001 |

Note: Hemorrhagic infarction type 1 was defined by small petechiae along the margins of the infarction, and type 2 was defined by more confluent petechiae within the infarction area. Parenchymal hematoma, type 1 was defined by one or more blood clots in 30% or less of the infarcted area with a mild space-occupying effect, and type 2 was defined by blood clots in more than 30% of the infarcted area with a clinically significant space-occupying effect. The modified Rankin scale of functional disability ranges from 0 (no symptoms) to 6 (death).

Abbreviations: CRP, C-reactive protein; CT, computed tomography; ICU, Intensive care unit; NIHSS, the National Institutes of Health Stroke Scale range from 0 to 42, with higher scores indicating a greater deficit.
Our study suggests that recanalization result did not have an impact on medical complications. This finding indicates that not only successful reperfusion but also patient-related factors such as comorbidities, advanced age and frailty as well as stroke severity also have an important role in predicting medical complications and outcome after stroke. In the present patient population, medical complications were associated with unfavorable outcomes including prolonged hospital LOS and deterioration of the functional capacity. Patients with medical complications were also less frequently discharged home. Since these issues are strongly associated with the costs of stroke, there is also an economic aspect to medical complications. Our study setting does not allow us to provide any causality between the complications and adverse events. However, most of the risk factors were highly related to comorbidities and stroke severity, which emphasizes the importance of patient selection to diminish undesirable outcomes. Deterioration in functional capacity after EVT is an unwanted condition and these patients may suffer from low quality of life. Nearly half of the patients with medical complications were bedridden or dead at 90 days after the event.

4.2 | Limitations of the study

This study has several limitations. This is a single-center retrospective study, which is a limitation. However, three experienced neurointerventional radiologists performed all the EVTs in our hospital during the study period. Annual number of procedures (average 78 EVT/year during the study period) is adequate to maintain high quality. We also have a standardized protocol, including stroke unit and ICU for optimal care of EVT patients. Unfortunately, we missed data of 50 patients during the follow-up period, which reduced the power of our data to assess the functional outcome at 90 days. Due to the retrospective study design, there also might be peri- and post-procedural factors we were not able to report, which may have an influence on outcome. For example, we did not include the measurements of blood pressure into the analysis. However, we use standardized protocol for blood pressure management and maintain systolic blood pressure (SBP) between 160 and 200 mmHg prior to reperfusion, except after intravenous thrombolysis target of SBP is between 160 and 185 mmHg. After successful reperfusion (TICI 2b-3) target of SBP is below 140 mmHg. Additionally, there is no control group in this study, since nowadays EVT is standard of care in ischemic stroke. Our study demonstrates an association between medical complications and unfavorable outcome but we are not able to determine other significant factors influencing the outcome. We do not disclose whether medical complications are an independent risk factor for unfavorable outcome. We focused on medical complications and therefore did not include the analysis of symptomatic intracerebral hemorrhage or consequences of neurological complications into this study. The strength of this study is generalizability of the results to a broad range of patients since we also included posterior circulation arterial occlusion patients.

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CONFLICT OF INTEREST

None of the authors have conflict of interest and this study did not receive any funding.

CONCLUSION

Medical complications are common after EVT among unselected stroke patients. Both comorbidity and stroke severity have an influence on medical complications. Recognition of risk groups for complications is essential when aiming to improve the outcome after EVT.

DATA AVAILABILITY STATEMENT

n/a

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