Analysis of Workflow and Time to Treatment on Thrombectomy Outcome in the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) Randomized, Controlled Trial

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**Background**—The Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trial used innovative imaging and aggressive target time metrics to demonstrate the benefit of endovascular treatment in patients with acute ischemic stroke. We analyze the impact of time on clinical outcome and the effect of patient, hospital, and health system characteristics on workflow within the trial.

**Methods and Results**—Relationship between outcome (modified Rankin Scale) and interval times was modeled by using logistic regression. Association between time intervals (stroke onset to arrival in endovascular-capable hospital, to qualifying computed tomography, to groin puncture, and to reperfusion) and patient, hospital, and health system characteristics were modeled by using negative binomial regression. Every 30-minute increase in computed tomography-to-reperfusion time reduced the probability of achieving a functionally independent outcome (90-day modified Rankin Scale 0–2) by 8.3% \( (P=0.006) \). Symptom onset-to-imaging time was not associated with outcome \( (P>0.05) \). Onset-to-endovascular hospital arrival time was 42% (34 minutes) longer among patients receiving intravenous alteplase at the referring hospital (drip and ship) versus direct transfer (mothership). Computed tomography-to-groin puncture time was 15% (8 minutes) shorter among patients presenting during work hours versus off hours, 41% (24 minutes) shorter in drip-ship patients versus mothership, and 43% (22 minutes) longer when general anesthesia was administered. The use of a balloon guide catheter during endovascular procedures shortened puncture-to-reperfusion time by 21% (8 minutes).

**Conclusions**—Imaging-to-reperfusion time is a significant predictor of outcome in the ESCAPE trial. Inefficiencies in triaging, off-hour presentation, intravenous alteplase administration, use of general anesthesia, and endovascular techniques offer major opportunities for improvement in workflow.

**Clinical Trial Registration**—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01778335. (Circulation. 2016;133:2279-2286. DOI: 10.1161/CIRCULATIONAHA.115.019983.)

**Key Words:** cerebrovascular disorders ■ emergency treatment ■ endovascular procedures ■ stroke ■ thrombolytic therapy
The Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trial provided evidence of the benefit of endovascular treatment in patients with moderate to severe ischemic stroke. The trial was based on the premise that patients with large-vessel occlusion of the anterior circulation with small to moderate infarct core and moderate to good collaterals identified on computed tomography (CT)-based imaging would benefit most from endovascular treatment if reperfusion was achieved quickly after imaging. In the ESCAPE trial, brain and neurovascular imaging identified favorable physiology; the clock started ticking from first imaging, the point of clinical decision making.

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In these prespecified secondary analyses, we analyze the effect of time from stroke symptom onset to imaging, time from imaging to reperfusion, and time from stroke symptom onset to reperfusion on clinical outcome among patients who received endovascular treatment in the ESCAPE trial. To reduce the inefficiencies in workflow that prolong the delivery of treatment and subsequent reperfusion, the ESCAPE trial used an active quality improvement process that provided site guidance on rapid image acquisition and interpretation, quick transfer to the angiography suite, and fast endovascular techniques. This quality improvement process contributed to the trial achieving highly efficient workflow metrics. Nonetheless, by recognizing that inefficiencies still exist, strategies for further improvement can be formulated. We analyzed patient, hospital, and health system characteristics associated with inefficiencies in workflow, ie, increase in interval times from stroke symptom onset to arrival in the emergency department, to imaging, to treatment administration, and to reperfusion.

Methods

The ESCAPE trial (clinicaltrials.gov NCT01778335) was an investigator-initiated multicenter randomized, controlled trial testing the additional benefit of modern endovascular treatment in comparison with guideline-based standard of care. The trial screened patients fulfilling clinical eligibility criteria if they presented within 12 hours of stroke symptom onset and then included them only if they met neurovascular imaging criteria. The trial enrolled 316 patients from 22 sites across 3 continents between February 2013 and October 2014.

The drive to optimal workflow began with site selection. Sites were selected only after documentation of efficient workflow demonstrated by 5 cases showing a CT-to-groin puncture time of <60 minutes and CT-to-reperfusion time of <90 minutes. All sites were visited in person. In half of the sites where it was permitted by local research ethics boards or institutional review boards, a deferral of consent process was used. A CT-based imaging paradigm that included noncontrast CT and multiphase CT angiography was designed to allow for quick acquisition and interpretation. The quality improvement process focused on achieving a qualifying CT-to-groin puncture time of ≤60 minutes and a qualifying CT-to-reperfusion time of ≤90 minutes through frequent in-person and Web-based teaching aids. Workflow and imaging data were analyzed weekly and frequent feedback provided to all sites through Web-based teleconferences.

The trial collected data on multiple events in the workflow from stroke symptom onset to reperfusion including time of stroke symptom onset, arrival in the emergency department of the endovascular-capable hospital, baseline imaging, randomization, intravenous tissue plasminogen activator (alteplase) administration, randomization, groin puncture, and reperfusion. Among patients who were referred to the endovascular-capable hospital from another hospital, data were collected on whether intravenous alteplase was administered before arrival in the emergency department of the endovascular-capable hospital (drip and ship) or after qualifying CT at the endovascular-capable hospital. Hospital arrival was defined as arrival at the emergency department of the endovascular-capable hospital. Decision on trial enrollment occurred only after imaging was performed at the endovascular-capable hospital. Baseline imaging time was defined as the time of the first slice of noncontrast CT head before randomization performed at the endovascular-capable hospital (qualifying CT). This definition ensured that the workflow metrics CT-to-groin puncture and CT-to-reperfusion time captured the time taken to acquire and interpret imaging. Reperfusion time was defined as time of first reflow into the middle cerebral artery territory. Data were collected on pertinent patient, hospital, and health system characteristics that can potentially influence workflow, including on (between 8 am and 5 pm on weekdays) versus off hours (before 8 am or after 5 pm on weekdays or on a weekend), anticoagulation use before stroke onset, use of general anesthesia, use of guide catheters as part of endovascular technique, difficulty in accessing target thrombus (left versus right anterior circulation), and country of enrolling site.

A flow chart showing steps in the ESCAPE trial leading up to treatment administration is shown in Figure 1.

Statistical Analyses

We considered 4 specific interval times: onset to emergency department arrival, emergency department arrival to qualifying CT scan, qualifying CT scan to groin puncture, and groin puncture to reperfusion. When reperfusion was not achieved, the reperfusion time was considered missing and was not imputed. Interval times from stroke symptom onset to first reperfusion are reported using medians and interquartile range (Table). All time intervals have skewed data distributions (nonnormal; Figure 1 in the online-only Data Supplement). A graphical examination of the residuals from linear regression revealed that the assumption of normality of residuals was not tenable for the time interval data, despite attempting a variety of transformations. We therefore investigated the use of generalized linear regression models for modeling the time interval data as discrete count data. Specifically, we examined whether Poisson regression, negative binomial regression, or gamma regression could provide the best fit to the data. Information theory approaches such as likelihood ratio test and Akaike information criterion were used to determine the regression model with the best fit to the data. To assess the relationship between patient, hospital, and health system characteristics as predictors of longer interval times, a negative binomial regression provided the best fit to the data. Therefore incidence rate ratios are reported for predictor variables associated with prolongation in each interval time after adjusting for other prespecified variables (Figure 2).

Logistic regression models were used to estimate the probability of functionally independent outcome (modified Rankin Scale 0–2 at 90 days) based on time from stroke symptom onset to qualifying CT, stroke symptom onset to first reperfusion, and qualifying CT to reperfusion after adjusting for age, sex, baseline National Institutes of Health Stroke Scale, occlusion site, baseline Alberta Stroke Program Early CT Score (ASPECTS), intravenous alteplase administration (and time from stroke symptom onset to qualifying CT when the predictor time variable was time from qualifying CT to reperfusion). Finally, because the primary outcome of the ESCAPE trial was the common odds ratio (shift analysis), similar analyses were performed for all other cut points on the ordinal modified Rankin Scale at 90 days. Statistical analysis was performed in R version 3.2.1 (R Development Core Team, 2014) and Stata/MP version 14.0 (StataCorp LP). Statistical significance was assessed at α<0.05 in all analyses.

Results

Interval times for trial workflow are described in the Table. Predictors of prolonged time intervals are shown in Figure 2. Time from stroke symptom onset to arrival in the emergency department of the endovascular-capable hospital was, on average, 42% (34 minutes) longer among patients who received
intravenous alteplase at the referring hospital and were subsequently transferred to the endovascular-capable hospital (drip and ship) in comparison with patients who were directly transferred to the endovascular-capable hospital (direct to mothership). Similarly, time from emergency department arrival to qualifying CT was, on average, 40% (8 minutes) longer among patients treated by the drip-and-ship paradigm than among patients who were transferred direct to mothership.

Time from qualifying CT to groin puncture was, on average, 15% (8 minutes) shorter among patients who presented to the endovascular-capable hospital during on hours versus those presenting during off hours. In patients who received

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Table. Interval Times in the Workflow of the ESCAPE Trial

<table>
<thead>
<tr>
<th>Workflow Time Intervals</th>
<th>N*</th>
<th>Median, min</th>
<th>Interquartile Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke symptom onset to arrival in emergency department of endovascular-capable hospital</td>
<td>308</td>
<td>107.5</td>
<td>49.5–224</td>
</tr>
<tr>
<td>Stroke symptom onset to qualifying CT</td>
<td>311</td>
<td>135</td>
<td>76–244</td>
</tr>
<tr>
<td>Stroke symptom onset to randomization</td>
<td>314</td>
<td>174</td>
<td>119–285</td>
</tr>
<tr>
<td>Stroke symptom onset to first reperfusion†</td>
<td>145</td>
<td>241</td>
<td>176–359</td>
</tr>
<tr>
<td>Arrival in emergency department of endovascular-capable hospital to qualifying CT</td>
<td>311</td>
<td>19</td>
<td>11–29</td>
</tr>
<tr>
<td>Qualifying CT to groin puncture†</td>
<td>161</td>
<td>51</td>
<td>39–68</td>
</tr>
<tr>
<td>Groin puncture to first reperfusion†</td>
<td>144</td>
<td>30</td>
<td>18–45.5</td>
</tr>
</tbody>
</table>

CT indicates computed tomography.

*Data available after central adjudication of all interval times.
†Endovascular group only
intravenous alteplase and endovascular treatment (n=109),
time from qualifying CT to groin puncture was, on aver-
age, 41% (24 minutes) shorter when intravenous alteplase
was administered before emergency department arrival (drip
and ship) than when intravenous alteplase was administered
after qualifying CT (direct to mothership). Administration
of general anesthesia was associated with prolongation of
CT-to-groin puncture time by 43% (22 minutes), on average,
in comparison with patients who did not receive general anes-
thetia. The use of a balloon guide catheter as part of the endo-
vascular technique was associated with shortened time from
groin puncture to first reperfusion by 21% (8 minutes), on
average, whereas a 5-point increase in the baseline National
Institutes of Health Stroke Scale (stroke severity) prolonged
this time by 11% (2 minutes). Deferral of consent, anticoag-
ulation use before stroke onset, and side of stroke were not
associated with differential workflow metrics in the trial.

The relationship between the probability of achieving
functionally independent outcome (modified Rankin Scale
[mRS] 0–2 at 90 days) and time from stroke symptom onset
to qualifying CT, qualifying CT to reperfusion, and stroke
symptom onset to reperfusion is shown in Figure 3. Every
30-minute increase in time from qualifying CT to reperfusion
is associated with an absolute decrease in the probability of
functionally independent outcome (mRS 0–2 at 90 days) by
8.3%, after adjusting for age, sex, baseline National Institutes
of Health Stroke Scale, occlusion site, baseline ASPECTS,
intravenous alteplase administration, and time from onset
to qualifying CT (P=0.006). No statistically significant

Discussion
In the ESCAPE trial, achieving a short imaging-to-reperfu-
sion time significantly improved the chance of achieving a
functionally independent outcome. There was no relationship
between outcome and stroke symptom onset-to-imaging time,
whereas the relationship between outcome and stroke symp-
tom onset to reperfusion was modest. These results support
acting rapidly and successfully on that information then predicts the outcome.1,3

Our results provide strong supportive evidence for the use of the imaging-to-puncture and imaging-to-reperfusion metrics as performance metrics and benchmarks for administering endovascular therapy.6,8 The finding that there is no relationship between clinical outcome and time from stroke symptom onset to qualifying CT should not be overinterpreted. All time delays before imaging matter.6,10,11 Stroke symptom onset time, however, is often inaccurate. Reasons include the fact that a majority of stroke patients are older and live alone, thereby having unwitnessed symptom onset; many strokes happen when patients are sleeping; many patients have fluctuating symptoms; and, in some cases, the witness is unable to recall the precise time of onset. Stroke symptom onset to imaging or reperfusion time is probably a less accurate measure of stroke physiology than imaging. Moreover, the ESCAPE trial design limited enrollment to patients with small to moderate ischemic core on imaging regardless of the time from stroke symptom onset. Although not captured in the trial, we suspect that the proportion of eligible patients with beneficial physiology on imaging dropped with increasing time from stroke symptom onset to qualifying CT.12

Several factors contribute to the speed of treatment. The ESCAPE trial used an intensive quality improvement process focused on quick, reliable imaging and efficient workflow from imaging to reperfusion with targets of qualifying CT-to-groin puncture time of <60 minutes and a CT-to-reperfusion time of <90 minutes. These workflow metrics are the fastest reported in patients with acute disabling ischemic stroke and significantly better than those required by the recent Multisociety Consensus Quality Improvement Guidelines for Intravenous therapy.6,8,13–19 The trial enrollment rate of 1.44 subjects per site per month, among the highest in recent acute stroke trials, at 22 sites on 3 continents attests to the generalizability of the workflow metrics achieved in the trial.1 Nonetheless, our analysis identified inefficiencies. Among these, transport of patient from first contact to endovascular-capable hospital (drip and ship versus direct to mothership paradigms), patient arriving at endovascular-capable hospital during off hours, intravenous alteplase administration in endovascular-capable hospitals, general anesthesia before endovascular procedure, and not using balloon guide catheters during the endovascular procedure represent opportunities for improvement.6,9,13

As in previous studies, we show that workflow was less efficient during off hours.6,9,13 Although the low number of patients with stroke currently eligible for endovascular treatment might make it challenging to have 24/7 in-house interventional teams, centralized hub-and-spoke models of stroke care, by increasing patient volumes in hub hospitals, could potentially make these changes pragmatically viable. Akin to multiple previous studies, we show that the use of general anesthesia is associated with longer times and prolonged workflow.6,13,20,21 General anesthesia is often unnecessary for thrombectomy and was used in only 9% of patients in the ESCAPE
trial. The endovascular procedure itself is challenging, more so in patients with difficult access to the target thrombus. As shown in previous technical reports, our data suggest that the use of balloon guide catheters may potentially lead to quick and efficient recanalization.22 Finally, although deferral of consent was used in some patients, this process itself was not measurably associated with improvement in workflow.

Administration of intravenous alteplase is standard of care in patients with acute ischemic stroke presenting within 4.5 hours of symptom onset.23,24 The ESCAPE trial stressed the need for a parallel workflow in endovascular-capable hospitals aimed at delivering intravenous alteplase to eligible patients without in any way delaying the patient’s transport to the angiography suite. Strategies included randomization before international normalized ratio results, because alteplase decision making was independent of ESCAPE randomization, administering alteplase bolus and infusion while the technologist was preparing the patient for CT angiography, and transferring the patient to the angiography suite without waiting for a clinical response to intravenous alteplase. Despite these measures, our analysis reveals that alteplase administration was associated with longer times from qualifying CT to groin puncture, suggesting that workflow may not have been in parallel in many patients.6 Novel thrombolytic agents such as intravenous tenecteplase, with its potentially faster treatment administration protocol as an intravenous bolus rather than infusion over 60 minutes, may help improve workflow.25,26

For endovascular-eligible patients identified on imaging, who are also eligible to receive intravenous alteplase, a focus on improving the first imaging-to-groin puncture (picture to puncture) metric should mirror ongoing efforts at improving the door-to-needle metric.6,8,27

The longer time from stroke symptom onset to emergency department arrival (at endovascular-capable tertiary hospitals) in the drip-and-ship treatment paradigm (intravenous alteplase before endovascular hospital emergency department arrival) in comparison with the direct to mothership approach is well known.1,28 Improving interval times is a complex system issue that must take into account geographical distributions and staffing patterns of primary and tertiary hospitals, transport times to these hospitals from first patient contact and with the drip-and-ship paradigm, mandating short (ideally ≤30 minutes) door-in to door-out times.9,18,29,30 Depending on the extent of centralization of stroke services, each health system may identify different solutions to minimize the time from first contact to reperfusion.

In conclusion, data from the ESCAPE trial support a refinement of the now well-known onset-to-treatment paradigm for acute stroke treatment. We show that the onset-to-reperfusion time epoch can now be broken up into 2 epochs, ie, time from onset to imaging and from imaging to reperfusion. These time epochs now provide a model for understanding the role of time and imaging selection. The first time epoch may determine who is eligible for therapy. The second time epoch, ie, imaging to reperfusion (treatment), determines who does well from therapy. Speed of treatment can be achieved in dedicated stroke centers with teamwork, parallel workflow, and a focus on quality improvement. Inefficiencies in triaging systems, presentation during off hours, intravenous alteplase administration, use of general anesthesia, and endovascular techniques offer major opportunities for improvement. Endovascular-capable hospitals should identify eligible patients by using quick and reliable imaging techniques and focus on achieving reperfusion as quickly and efficiently as possible.

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Disclosures

Drs Menon, Sajobi, Goyal, and Hill had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors fulfill all 4 ICMJE criteria for authorship and are submitting the authorship forms. Dr Roy reports grants and personal fees from University of Calgary; during the conduct of the study. Dr Williams reports personal fees from Boehringer Ingelheim, Bayer, Bristol Myers Squibb and Daliichi Sankyo outside the submitted work. Dr Demchuk reports grants and personal fees from Medtronic during the conduct of the study. Dr Lowerison reports other from Clinical Research Unit during the conduct of the study. Dr Poppe reports personal fees from Covidien and Pfizer-BMS outside the submitted work. Dr Frei reports personal fees from Covidien, Stryker, Penumbra, Microvention, and Siemens during the conduct of the study. Dr Thornton reports personal fees from Neuravi, Galway and Ireland outside the submitted work. Dr Baxter reports personal fees from Penumbra, Stryker Neurovascular, Covidien (MedTronics), Rapid Medical, and Silk Road Medical outside the submitted work. Dr Jovin reports personal fees from Covidien and Stryker during the conduct of the study. Dr Hill reports grants from Covidien (Medtronic), Alberta Innovates Health Solutions, Heart & Stroke Foundation, Hotchkiss Brain Institute, CSPIN Network (ICRH-CIHR), Calgary Stroke Program, DCNS, University of Calgary, nonfinancial support from Alberta Health Services, during the conduct of the study; personal fees from Merek, nonfinancial support from Hoffmann-La Roche Canada Ltd., outside the submitted work. Dr Menon reports a patent pending on systems of triage in patients with Acute Ischemic Stroke and board membership of QuikFlo Health Inc. Dr Goyal reports grants from Covidien, personal fees from Covidien, during the conduct of the study. In addition, Dr Goyal has a patent Systems of stroke diagnosis licensed to GE Healthcare. The other authors report no conflicts.

References


**CLINICAL PERSPECTIVE**

Data from the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trial support a refinement of the now well-known onset-to-treatment paradigm for acute stroke treatment. We show that the onset-to-treatment time epoch can now be broken up into 2 epochs, ie, time from onset to imaging and from imaging to reperfusion. These time epochs now provide a highly physiological model for understanding the role of time and imaging selection. The first time epoch, ie, stroke onset to imaging, determines who is eligible for therapy. The second time epoch, ie, imaging to reperfusion (treatment), determines who does well from therapy. The ESCAPE trial reports on data from a new era associated with the use of mechanical stent retrievers and an explicit focus on improving workflow. Although workflow metrics within the trial are the fastest reported to date, we are still able to identify inefficiencies including delay around intravenous alteplase administration, off-hour presentation, general anesthetic use, and specific endovascular techniques that suggest opportunities toward further improvement in workflow and consequently better outcome. The ESCAPE trial data presented here are the first prospective and comprehensive analyses of inefficiencies that continue to exist in the modern acute ischemic stroke treatment workflow. Health systems can focus on transporting patients with disabling symptoms and proximal occlusions as quickly as possible to endovascular-capable hospitals. Physicians in these hospitals can then identify patients with beneficial physiology by using imaging and focus on delivering treatment to these patients quickly and efficiently. A focus on improving imaging-to-groin puncture and imaging-to-reperfusion time metrics should mirror ongoing efforts at improving the door-to-needle time metric in tertiary hospitals.
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SUPPLEMENTAL MATERIAL

Supplemental Figure 1: Skewed distribution of the four pre-specified interval times used in the analysis.
Supplemental Figure 2: Estimated probability of achieving functionally independent outcome [modified Rankin Scale (mRS) 0-2] at 90 days by time from stroke symptom onset to randomization in patients in the control and intervention arm of the ESCAPE trial (adjusted for age, sex, baseline NIHSS, occlusion site, baseline ASPECTS, intravenous alteplase administration). No statistically significant relationship is noted between stroke symptom onset to randomization time and outcome in either arm of the trial (p>=0.05). Test for interaction between stroke symptom onset to randomization time and treatment allocation is non-significant (p=0.63).
Supplemental Table 1: Relationship between probability of achieving each mRS cut-point and time from stroke symptom onset to qualifying CT, qualifying CT to reperfusion and stroke symptom onset to reperfusion (after adjusting for age, sex, baseline NIHSS, occlusion site, baseline ASPECTS and intravenous alteplase administration).

| Relationship between Time from Stroke Symptom Onset to Imaging (Intervention arm) |
|-----------------------------------------------|-----------------|-----------------|-----------------|
| mRS Cut-point | Odds Ratio (for every 30 min increase in time) | 95% CI | p value |
| 0 vs. 1-6 | 1 | 0.918-1.089 | 0.999 |
| 0-1 vs. 2-6 | 1.022 | 0.960-1.089 | 0.494 |
| 0-2 vs. 3-6 | 0.964 | 0.907-1.023 | 0.232 |
| 0-3 vs. 4-6 | 0.971 | 0.915-1.031 | 0.336 |
| 0-4 vs. 5-6 | 0.925 | 0.864-0.991 | 0.026 |
| 0-5 vs. 6 | 0.976 | 0.901-1.057 | 0.557 |

| Relationship between Time from Qualifying Imaging to Reperfusion (Intervention arm) |
|-----------------------------------------------|-----------------|-----------------|-----------------|
| mRS Cut-point | Odds Ratio (for every 30 min increase in time) | 95% CI | p value |
| 0 vs. 1-6 | 0.878 | 0.606-1.271 | 0.49 |
| 0-1 vs. 2-6 | 0.774 | 0.582-1.029 | 0.078 |
| 0-2 vs. 3-6 | 0.662 | 0.493-0.890 | 0.006 |
| 0-3 vs. 4-6 | 0.724 | 0.534-0.981 | 0.037 |
| 0-4 vs. 5-6 | 0.908 | 0.587-1.402 | 0.662 |
| 0-5 vs. 6 | 1.057 | 0.572-1.954 | 0.859 |

| Relationship between Time from Stroke Onset to Reperfusion (Intervention arm) |
|-----------------------------------------------|-----------------|-----------------|-----------------|
| mRS Cut-point | Odds Ratio (for every 30 min increase in time) | 95% CI | p value |
| 0 vs. 1-6 | 0.965 | 0.864-1.077 | 0.526 |
| 0-1 vs. 2-6 | 0.978 | 0.899-1.064 | 0.604 |
| 0-2 vs. 3-6 | 0.912 | 0.834-0.997 | 0.044 |
| 0-3 vs. 4-6 | 0.940 | 0.855-1.032 | 0.198 |
| 0-4 vs. 5-6 | 0.913 | 0.812-1.027 | 0.13 |
| 0-5 vs. 6 | 0.959 | 0.833-1.105 | 0.567 |