Propensity for performing interventions in pre-hospital trauma management – a comparison between physicians and non-physicians

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Abstract

Background: In 2005, the Advanced Life Support (ALS) teams delivering pre-hospital care in RegionSkane in southern Sweden received additional support by physicians, who were part of “Pre-hospital acute teams” (PHAT). The study objective is to compare the incidence of pre-hospital medical interventions for trauma-patients cared for by conventional ALS teams and patients who received additional support by PHAT.

Methods: Trauma patients with Injury Severity Score (ISS) > 9 were identified retrospectively in the national quality registry KVITTRA at three hospitals in RegionSkane, for the time period October 2005 to December 2008. Interventions include e.g. tracheal intubation, administration of i.v. fluids, neck immobilization and spine board usage. Confounding effects from trauma severity, trauma mechanism, vital parameters, age and sex were addressed in multivariate models.

Results: Data from 202 cases was included. 9 pre-hospital interventions were assessed. The incidence of endotracheal intubation and immobilisation of extremities was higher among patients in the PHAT-group compared to the ALS-only group (16.3% vs. 6.9%, p = 0.034) and (12.8% vs. 4.3%, p = 0.027) respectively. PHATs presence remained a significant predictor of these interventions also after taking confounding factors into account (OR 5.5, CI 1.5-19.7) and (OR 3.2 CI 1.0-9.8). PHAT was involved in a greater proportion of cases with < 50.0% of survival (19.8% vs. 12.1%, p = 0.134). The average ISS was higher among cases receiving PHAT support in strata ISS 16-24 and ISS > 24 than cases in corresponding strata cared for by ALS teams alone (ISS 20.0 vs. 17.0, p = 0.048 and ISS 34.0 vs. 29.0, p = 0.019).

Conclusions: The incidence of endotracheal intubation and immobilization of extremities was greater among patients supported by PHAT, compared to patients cared for by ALS teams alone. This finding has to be interpreted in the light of a selection-bias where PHAT support was directed to more severely injured patients.

Keywords: Trauma, Medical services, Emergency, Emergency care, Prehospital

Introduction

Scientific evaluation of physicians caring for trauma patients in the pre-hospital setting is not fully conclusive [1]. There is some support for a beneficial effect of their presence [2], despite of the contradictory results of a large multi-centre study [3]. A randomized controlled trial addressing the subject suggests that physicians adhere to pre-hospital intervention protocols better and succeed in a larger number of interventions than nurses do. The same study showed lower mortality rates among patients receiving pre-hospital care from physicians [4]. Beneficial effects of physician presence have also been shown for patients suffering blunt head trauma [5]. Other studies have failed to show a difference [6]. Several studies show that physicians tend to be directed to trauma of higher severity [7-9].

A recent study comparing physicians and ambulance nurses highlighted several physician-specific competencies [10]. Others have shown that trauma-patients cared for by physicians are more prone to be treated and

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discharged at the trauma scene [11]. Still others argue
ment that it is more important to identify need and to
perform an intervention correctly, than which profession
possesses a certain competence [12]. Evaluating physi-
cians in pre-hospital care by addressing outcomes has
been questioned, as intra-hospital factors might confound
results [10].

Advanced Life Support (ALS) is the pre-hospital sys-
tem used in the country council RegionSkane in south-
ern Sweden. The ALS-teams consist of a nurse and an
emergency medicine technician. Starting in 2005, the
ALS teams received support by "Pre-hospital acute teams"
(PHAT), staffed by a physician and a nurse. One PHAT-
team was stationed at each of the general hospitals in
Helsingborg, Kristianstad, Lund and Malmoe. PHAT was
introduced at slightly different times at the different
hospitals (Helsingborg general hospital: October 2005,
Kristianstad general hospital: March 2006, Skane University
hospital, Lund: January 2005 and Malmoe general hos-
pital: October 2006). In December 2008, PHAT was abol-
ished simultaneously in all hospitals due to a perceived lack
of benefits. From October 2005 to December 2008 PHAT
was the only means by which ALS teams could receive pre-
hospital support by a physician.

The study objective is to evaluate whether the incidence
of pre-hospital interventions differs between trauma-
patients cared for by conventional ALS teams compared
to patients who received additional support by PHAT.
Bearing work performed by others in mind, the authors
believe that the incidence of interventions would possibly
be higher among patients who received support by PHAT.
The present study will add important information about
pre-hospital physician support under Swedish conditions,
which (according to the knowledge of the authors) has
not yet been scientifically evaluated.

Methods
Study design
The study was conducted as a register study, utilizing data
retrieved from the quality registry KVITTRA (Kvalitet i
Traumavården). Trauma patients were identified in the
local KVITTRA registries of Helsingborg general hospital,
Kristianstad general hospital and Skane University hos-
pital, Lund. Malmoe general hospital was not connected
to KVITTRA and was therefore not included.

Outcomes
The main outcome of the study was differences in inci-
dence of pre-hospital medical interventions between
trauma-patients cared for by conventional ALS teams
and trauma-patients that received additional support
from PHAT. Differences in 30-day mortality were the
secondary outcome.

Setting
RegionSkane is a country council in southern Sweden,
populated by about 1 100 000 people, few of which live
further than 50 km from the closest hospital. There is
no full Level-I trauma centre in RegionSkane. Skane
University Hospital, Lund is the only hospital with ac-
to neurosurgery and thoracic surgery around the
clock, while both Skane University hospital, Lund and
Malmoe general hospital have access to vascular surgery.
Malmoe general hospital is the only hospital having access
to hand-surgery around the clock. Other hospitals in the
region have to refer patients to these levels of care.

Physician members of PHAT were senior residents or
specialists in anesthesiology, emergency medicine, in-
ternal medicine or surgery. Exceptions were one primary
care physician and one otolaryngologist. All had undergone
ATLS training, as well as specific training provided by
RegionSkane. PHAT was dispatched either upon request by
the ALS teams, by the alarm-center staff (in accordance
with criteria stated in the list of PHAT dispatching criteria)
or on PHATs own accord. The latter was possible as
PHAT had access to radio-communication between the
alarm-center and the ALS teams. PHAT could also give
advice over telephone. Empirical knowledge suggests that
PHAT was consulted over telephone in the majority of
trauma cases of ISS > 15.

List of PHAT dispatching criteria

1. Cardiac arrest or suspected cardiac arrest
2. Suspected very traumatized patient
3. Unconscious patient with obvious signs of affected
   breathing and circulation
4. Lack of ambulances in the vicinity
5. Request from a conventional ALS-team
6. Need for care directorship or at an incident with
   more than five patients suffering severe trauma
7. PHAT personnel find dispatching necessary,
   e.g. for educational purposes

KVITTRA is a national quality registry for trauma-care,
enscaping trauma-patients who die within 30 days of
the trauma, undergo surgery within 24 hours, receive care
in the ICU or are transported to a regional hospital. Data
is registered in KVITTRA prospectively. For each hospi-
tal in RegionSkane connected to KVITTRA, one person
(nurse or secretary) is responsible for the registrations.
Only cases with ISS > 9 are exported to the national regis-
try. In addition to pre-hospital interventions, KVITTRA
also includes vital parameters, primary- and secondary in-
jury mechanisms (ICD-9/10), AIS, ISS, TRISS and some
information about intra-hospital interventions (e.g. time
to x-ray investigation). Registered vital parameters are
measured in the pre-hospital setting. KVITTRA does not
contain data on the anatomic distribution of injuries. In
Region Skane, many cases with ISS < 10 are registered in KVITTTRA as they are referred to Malmoe for hand-surgery. Due to low priority of registrations in KVITTTRA at Skane University Hospital, Lund, only 8 months (Jan-Aug 2008) of the study period were covered in the Lund registry. All pre-hospital interventions registered in KVITTTRA could be performed by PHAT physicians as well as by the ALS teams, except from blood transfusion, which was therefore not evaluated.

Inclusion criteria
Patients with Injury Severity Score (ISS) > 9, who were registered in KVITTTRA at the three general hospitals of Helsingborg and Kristianstad, and Skane University hospital, Lund during the period PHAT was in use and who arrived to the hospital by ambulance were eligible for study. Cases subject to incomplete data on 30-day mortality, physician attendance or primary trauma-mechanism were excluded.

Determining sample size
To be able to detect a 20% effect size, each study arm has to contain 70 cases according to the formula below:

\[
n = \frac{2(Z_a + Z_{1-\beta})^2 \Delta^2}{\alpha^2}
\]

\(n\) = sample size
\(Z_a = 1.96\) for two sided effect, \(p = 0.05\) level
\(Z_{1-\beta} = 0.8416\) for 80% power
\(\alpha = 0.40\) (estimated sample SD)
\(\Delta = \text{effect size}\)

All patients that met the inclusion criteria were eligible for inclusion, in order not to introduce additional bias.

Data collection
Data on physician attendance, pre-hospital interventions and baseline characteristics in the form of 30-day mortality, in-patient length of stay (IPLOS), time spent on the trauma-scene, trauma-mechanism (according to ICD9/10), age, sex, vital parameters (respiratory rate, Glasgow Coma Scale and systolic blood-pressure), ISS and TRISS were collected from KVITTTRA and merged using Microsoft Office Excel® Mac 2011 (Microsoft Corporation, USA). Statistical analysis was performed using IBM® SPSS® Statistics 19. Prevented likely deaths were quantified as surviving cases with probability of survival <50.0% and unlikely deaths were defined as cases who died despite of having >50.0% probability of survival (based on the TRISS methodology).

Differences in baseline characteristics and pre-hospital interventions
Continuous variables were assessed for normality using Shapiro-Wilks test. Differences in number of patients with low probability for survival, prevented likely deaths and unlikely deaths as well as ISS, age, time spent on the trauma scene and IPLOS were assessed using the Mann-Whitney U test. Comparison of the incidence of pre-hospital interventions was performed using the Chi2 test and Fisher exact test where appropriate. Due to established dispatching-criteria, a selection bias was expected. In order to compensate for part of this bias, binary logistic regression models addressing confounding from age, sex, trauma severity (ISS), trauma mechanism, vital parameters and 30-day mortality were constructed.

Variables
ISS and age were categorized according to intervals used in the Major Trauma Outcome Study [13], i.e. ISS 10-15, ISS 16-24, ISS > 24 and age dichotomized at 55 years. Vital parameters were categorized according to intervals used in the Revised Trauma Score (RTS) methodology. However, some groups were merged due to their small size. Reference intervals in the model were: GCS score 13-15, Respiratory rate 10-29 breaths/min, ISS 10-15.

To enter the final model, a variable had to be more strongly associated with the outcome than \(p = 0.10\). Associations with \(p < 0.05\) were considered statistically significant. Trauma-mechanisms according to ICD-9/10 were manually classified as “blunt trauma” or “penetrating trauma” by one of the authors (MB).

Ethical approval for the study was granted to the ethical approval committee of Lund.

Results
Included patients
A total of 621 cases were registered in KVITTTRA at the three hospitals during the study period (Helsingborg, n = 247, Kristianstad, n = 115, Lund, n = 259). Of the 621 screened cases, 362 had an ISS < 10 and were not eligible for inclusion.

Of the 259 remaining cases, 1 did not arrive by ambulance, 21 lacked data on physician attendance, 29 lacked data on 30-day mortality, and 5 lacked data on trauma-mechanism. One unreasonable case was identified (registered as dead within 30 days but registered IPLOS was 172 days). These 57 cases were excluded and hence 202 patients entered the final analyses. From the previously stated formula for sample size calculation, this would be enough to detect an effect size of 19%.

Baseline characteristics
Out of the 202 cases, 86 (43%) patients received support from PHAT and 116 (57%) were cared for by the ALS teams alone. 22 (25.6%) cases receiving support by PHAT died within 30 days, compared to 18 (15.5%) cases in the other group (\(p = 0.076\)).
|                          | ISS 10-15 | ISS 16-24 | ISS > 24 | Total |
|--------------------------|-----------|-----------|----------|-------|
|                          | Non-physician (n = 38) | Physician (n = 31) | p | Non-physician (n = 47) | Physician (n = 25) | p | Non-physician (n = 31) | Physician (n = 30) | p | Non-physician (n = 116) | Physician (n = 86) | p |
| ISS (IQR)                | 13.0 (3.0) | 12.0 (3.0) | 0.29 | 17.0 (3.0) | 20.0 (5.5) | 0.048 | 29.0 (8.0) | 34.0 (16.5) | 0.019 | 17 (12) | 20 (16) | 0.34 |
| Age, years (IQR)         | 44.0 (36.8) | 47.0 (47.0) | 0.23 | 48.0 (37.0) | 48.0 (27.5) | 0.67 | 41.0 (33.0) | 37.0 (33.5) | 0.78 | 44 (35.8) | 44.5 (35.5) | 0.49 |
| Male                     | 26        | 25        | 0.25 | 28        | 16        | 0.71 | 22        | 23        | 0.61 | 76        | 64        | 0.18 |
| Female                   | 12        | 6         | 0.25 | 19        | 9         | 0.71 | 9         | 7         | 0.61 | 40        | 22        | 0.18 |
| Time on trauma scene, hh:mm (IQR) | 00:19 | 00:18 | 0.61 | 00:15 | 00:14 | 0.40 | 00:15 | 00:12 | 0.39 | 00:16 | 00:15 | 0.82 |
| (N missing)              | 00:11     | 00:14     | 0.00 | 00:10     | 00:11     | 0.00 | 00:11     | 00:14     | 0.00 | 00:10     | 00:14     | 0.00 |
| IPLOS, days (IQR)        | 5.5 (12.5) | 9.0 (13.0) | 0.058 | 4.0 (14.0) | 9.0 (19.0) | 0.083 | 13.0 (28.0) | 0.5 (24.5) | 0.27 | 5.5 (16) | 7.5 (18.3) | 0.24 |
| Penetr. trauma           | 2         | 2         | 1.0 | 3         | 1         | 1.0 | 0         | 4         | 0.053 | 5         | 7         | 0.26 |
| GCS (IQR)                | 15 (1)    | 15 (0)    | 0.32 | 14 (8)    | 15 (2.5)  | 0.032 | 13 (12)   | 6.5 (12)  | 0.302 | 14 (6.75) | 15 (8)    | 0.34 |
| Systolic b.p., mmHg (IQR) | 130 (42.8) | 139 (35) | 0.75 | 120 (41)  | 130 (54.5) | 0.16 | 100 (50)  | 105 (77.8) | 0.53 | 120 (41)  | 130 (51.5) | 0.18 |
| Resp. rate, breaths/min (IQR) | 20 (4) | 20 (4) | 0.73 | 16 (4)    | 20 (3.5)  | 0.001 | 20 (10)   | 16 (13.3) | 0.98 | 20 (4)    | 20 (4.25) | 0.17 |
| 30 day mort.             | 0 (0%)    | 1 (3.2%)  | 0.45 | 8 (17.0%) | 4 (16.0%) | 1.0 | 10 (32.3%) | 17 (56.7%) | 0.073 | 18 (15.5%) | 22 (25.6%) | 0.076 |
| N.o. cases with <50 pct prob. of survival | 0 (0%) | 0 (0%) | 0.47 | 1 (3.2%)  | 3 (10.0%) | 0.29 | 2 (1.7%)  | 3 (3.5%)  | 0.43 |
| Prevented likely deaths  | 0 (0%)    | 0 (0%)    | 1.0 | 1 (2.1%)  | 0 (0%)    | 0.47 | 1 (3.2%)  | 3 (10.0%) | 0.29 | 2 (1.7%)  | 3 (3.5%)  | 0.43 |
| Unlikely deaths          | 0 (0%)    | 1 (3.2%)  | 0.27 | 5 (10.6%) | 3 (12.0%) | 0.86 | 1 (3.2%)  | 4 (13.3%) | 0.15 | 6 (5.2%)  | 8 (9.3%)  | 0.254 |

Median and inter-quartile range (IQR). Mann-Whitney U test used for comparisons. Missing values indicated where appropriate.
Patients supported by PHAT had a significantly higher median ISS than patients cared for by ALS teams alone among cases with ISS 16-24 (20.0 vs. 17.0, \( p = 0.048 \)) and ISS > 24 (34.0 vs. 29.0, \( p = 0.019 \)). Median IPLOS for patients receiving support from PHAT and having ISS > 24 was less than for patients attended to by the ALS teams alone (0.5 days vs. 13.0 days, \( p = 0.27 \)). No statistically significant differences in patient age or time spent on the trauma scene were seen. 19.8% of patients cared for by PHAT had a probability of survival of <50.0%, compared to 12.1% for patients cared for by the ALS teams alone (\( p = 0.134 \)). 3.5% of patients in the PHAT-group survived despite of having <50.0% probability of survival, vs. 1.7% in the ALS-only group (\( p = 0.43 \)). 9.3% of patients in the PHAT-group died despite of having >50.0% probability of survival, compared to 5.2% in the ALS-only group (\( p = 0.254 \)). For further details, please see Table 1.

### Prehospital interventions

The incidence of endotracheal intubation was higher among patients supported by PHAT, compared to patients attended to by ALS teams alone (16.3% vs. 6.9%, \( p = 0.034 \)). This effect remained significant for patients with ISS > 24 (40.0% vs. 16.1%, \( p = 0.038 \)) upon subgroup analysis. The incidence of immobilization of extremities was also higher among patients attended to by PHAT (12.8% vs. 4.3%, \( p = 0.027 \)). A trend to higher incidence of administration of crystalline- and colloid fluids was also seen (52.3% vs. 39.7% (\( p = 0.074 \)) and 3.5% vs. 0.0% (\( p = 0.076 \)) respectively. Results above are not adjusted for confounding. One patient, who was cared for by the ALS teams only, was subject to blood transfusion according to the registry. This was outside the therapeutic possibilities of the ALS teams and is attributed to registration error. For further details, please see Table 2.

After taking confounding factors into account, the probability of endotracheal intubation remained higher in the PHAT-group compared to the ALS-only group (OR 5.5, CI 1.5-19.7). The same holds true for immobilization of extremity (OR 3.2 CI 1.0-9.8). No other significant differences between the compared groups were seen in the multivariate analysis. For further details, please see Table 3.

### Table 2 Incidence of pre-hospital interventions stratified according to trauma severity and in total

| Intervention                  | ISS 10-15 ALS only (n = 38) | PHAT (n = 31) | p | ISS 16-24 ALS only (n = 47) | PHAT (n = 25) | p | ISS > 24 ALS only (n = 31) | PHAT (n = 30) | p | Total ALS only (n = 116) | PHAT (n = 86) | p |
|-------------------------------|-----------------------------|---------------|---|-----------------------------|---------------|---|-----------------------------|---------------|---|------------------------|---------------|---|
| Nasal airway                  | 2                           | 1             | 1.0 | 1                           | 0             | 1.0 | 0                           | 2             | 0.24 | 3 | 3 | 0.70 |
| Oral airway                   | 0                           | 1             | 0.45 | 3                           | 1             | 1.0 | 2                           | 3             | 0.67 | 5 | 5 | 0.75 |
| Endotrach. intubation         | 0                           | 1             | 0.23 | 3                           | 2             | 1.0 | 5                           | 12            | 0.038 | 8 | 14 | 0.034 |
| Neck-immob.                   | 32                          | 1             | 0.74 | 32                          | 20            | 0.28 | 25                          | 21            | 0.33 | 89 | 68 | 0.69 |
| Spine board                   | 30                          | 23            | 0.64 | 26                          | 17            | 0.30 | 24                          | 18            | 0.14 | 80 | 58 | 0.82 |
| Immob. of extremity           | 2                           | 5             | 0.23 | 1                           | 2             | 0.28 | 2                           | 4             | 0.43 | 5 | 11 | 0.027 |
| Crystalline fluids            | 13                          | 15            | 0.23 | 14                          | 11            | 0.23 | 19                          | 19            | 0.87 | 46 | 45 | 0.074 |
| Colloid fluids                | 0                           | 0             | 0.00 | 0                           | 1             | 0.35 | 0                           | 2             | 0.24 | 0 | 3 | 0.076 |
| Hypertonic solution           | 0                           | 0             | 0.00 | 0                           | 0             | 0.00 | 0                           | 1             | 0.49 | 0 | 1 | 0.24 |

Chi2 and Fisher's exact test used for comparing incidence.

### Table 3 Adjusted probability for pre-hospital interventions

| Intervention               | Strength of association of PHAT presence to intervention (p) | OR for experiencing intervention if cared for by PHAT (CI) | Fit of regression model (Nagelkerke R²) |
|----------------------------|-------------------------------------------------------------|------------------------------------------------------------|----------------------------------------|
| Nasal airway               | ≥ 0.10                                                      | -                                                          | 0.092                                  |
| Oral airway                | ≥ 0.10                                                      | -                                                          | 0.225                                  |
| Endotracheal intubation     | 0.01                                                       | 5.5 (1.5-19.7)                                             | 0.521                                  |
| Neck-immobilisation        | ≥ 0.10                                                     | -                                                          | 0.464                                  |
| Spine board                | ≥ 0.10                                                     | -                                                          | 0.405                                  |
| Immobilisation of extremity| 0.041                                                      | 3.2 (1.0-9.8)                                              | 0.129                                  |
| Crystalline fluids         | ≥ 0.10                                                     | -                                                          | 0.115                                  |
| Colloid fluids             | ≥ 0.10                                                     | -                                                          | 0.576                                  |
| Hypertonic solution        | ≥ 0.10                                                     | -                                                          | 0.704                                  |

Probability is expressed as odds ratio (OR), normalised for confounding from age, sex, trauma severity, trauma mechanism, vital parameters and 30-day mortality. OR shown for associations \( p ≤ 0.10 \).
Discussion

The incidence of endotracheal intubation and immobilisation of extremities was higher among patients in the PHAT-group compared to the ALS-only group: 16.3% vs. 6.9% (p = 0.034) and 12.8% vs. 4.3% (p = 0.027) respectively. PHATs presence remained a significant predictor of these interventions also after taking confounding factors into account (OR 5.5, CI 1.5-19.7 and OR 3.2 CI 1.0-9.8, respectively). A trend to higher incidence of treatment with crystalline fluids (52.3% vs. 39.7%, p = 0.074) and colloids (3.5% vs. 0.0%, p = 0.076) was seen in the PHAT-group. No differences in fluid therapy were seen in the multivariate analyses. The main results gain some support from other studies [4,11].

Limitations include that telephone consultations were not adjusted for, but might have influenced the results. Furthermore, the lack of complete registrations in KVITTRA of Skane University Hospital, Lund during part of the study period imposes questions on data quality and also reduces the power of the study.

The presence of a selection-bias is indicated by a higher median ISS among cases of ISS 16-24 (20.0 vs. 17.0, p = 0.048) and ISS > 24 (34.0 vs. 29.0 p = 0.019) in the PHAT-group than corresponding strata within the ALS-only group. The bias most likely results from PHAT being directed to more severe cases due to its specific dispatching criteria (Table 1). The bias gains further support by the presence of a greater fraction of patients with low probability of survival (TRISS <50%) in the PHAT-group (3.5% vs. 1.7%). This is most evident among patients of ISS > 24 (10.0% vs. 3.2%, p = 0.29). Even though it affects the results, the selection bias was expected and gains support in the literature [7-9]. The shorter IPLOS for cases with ISS > 24 in the PHAT-group compared to corresponding cases in the ALS-only group (0.5 vs. 13.0 days, p = 0.27) is most likely explained by the higher mortality in this group.

The authors believe that the results can be interpreted in either of two ways. The first is that PHAT and the associated more aggressive pre-hospital treatment is not beneficial to patients, as it is associated with higher 30-day mortality and more unlikely deaths. The other interpretation is that the higher mortality is caused by a selection bias, together with factors influencing 30-day mortality not taken into account by the TRISS methodology (e.g. comorbidity). Even though an attempt to address the bias was made through stratifying the groups into ISS-intervals, this is most likely not enough to adequately discern subtle variation in risk within each stratum. Hence it still remains to be elucidated how much of the variation in pre-hospital treatment could be attributed to different competencies of the pre-hospital personnel.

Conclusion

The incidence of endotracheal intubation and immobilization of extremities was greater among patients who received support by PHAT compared to patients cared for by ALS teams alone, in the present study. Due to the presence of a selection bias caused by PHAT being directed to trauma of greater severity, it remains to be elucidated what proportion of the results could be explained by different competencies of the pre-hospital personnel. It is desirable to couple differences in the provision of pre-hospital care to functional outcomes in future studies, which would require organ-specific data as well as data on intra-hospital factors and patient co-morbidity.

Consent

Only anonymized data was analyzed and hence written consent was not obtained from individual patients. This procedure was supported by the decision from the regional ethical review board in Lund.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

MB was the principal investigator and took part in the formulating the research question, in the statistical analyses, in searching the literature and in the writing of the final article. LA took part in formulating the research question, in searching the literature and in commenting on the manuscript. KI was the supervisor of the project. KI commented on repeated versions of the manuscript. KI provided support to the two other authors and answered clinical as well as methodological questions. KI also granted access to the data material used and was granted ethical approval for the study. All authors read and approved the final manuscript.

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