INNOVATION REPORT NO 2

Fracture treatment in the Baltic Sea Region

Analysis of the registry data collected in the BFCC

Robert Wendlandt

UKSH, Department of Orthopedics and Trauma Surgery
University Medical Center Schleswig-Holstein

EUROPEAN UNION
EUROPEAN REGIONAL DEVELOPMENT FUND

Interreg Baltic Sea Region

BFCC Baltic Fracture Competence Centre

- Life Science Nord Management GmbH (Germany)
- Stryker Trauma GmbH (Germany)
- University Medical Center Schleswig-Holstein (Germany)
- University Medicine Greifswald (Germany)
- Sahlgrenska University Hospital (Sweden)
- ScanBalt fmba (Denmark)
- Lithuania University of Health Sciences (Lithuania)
- LifeScience Krakow Klaster (Poland)
- University Hospital in Krakow (Poland)
- University of Tartu (Estonia)
- Tartu Biotechnology Park (Estonia)
- Bone Index Finland Ltd. (Finland)
- BONESUPPORT AB (Sweden)

Fracture treatment in the Baltic Sea Region: Analysis of the registry data collected in the BFCC
Robert Wendlandt
UKSH, Department of Orthopedics
and Trauma Surgery
University Medical Center Schleswig-Holstein

Layout & graphic design
amt tipografia design gráfico
Anne Mayer-Tasch
Friedrichsdorf, Germany
https://amt.myportfolio.com/

Photos & illustrations
Shutterstock.com:
Spotmatik Ltd (p. 4), Guschenkova (p. 23)
Adobe Stock:
adam121 (p. 19), Saklakova (p. 20)
All unmarked illustrations: Anne Mayer-Tasch

Published in February 2019

Lead partner & publisher
Baltic Fracture Competence Centre
Life Science Nord Management GmbH
Legienstraße 40, 24103 Kiel, Germany
+49 431 90 89 68 58
Contact: Imke Schneemann
schneemann@lifesciencenord.de
www.lifesciencenord.de

www.bfcc-project.eu

Supported by:

Interreg Baltic Sea Region

EUROPEAN UNION

EUROPEAN REGIONAL DEVELOPMENT FUND

CONTENTS

BFCC—BALTIC FRACTURE COMPETENCE CENTRE

The Baltic Fracture Competence Centre (BFCC) is a pan-Baltic fracture cooperation network fostering innovation within fracture management. The project consortium consists of a transnational cross-sector partnership involving five hospitals, three companies from the medical technology industry, a university, three clusters and one technology transfer organization.

Due to an ageing society, the need for innovative products and clinical procedures for fracture treatment is increasing as a response to age-related fractures and co-morbidities such as osteoporosis, infections and non-unions. Innovations in fracture management must reduce the cost of care or clearly improve quality of care.

Clinicians will support the innovation process by identifying the clinical needs to ensure user-oriented product development. The collaboration between hospitals across countries will foster the innovation of clinical procedures through the exchange of best practice in fracture management influenced by different national, organizational and regulatory conditions.

However, clinicians and companies often lack insight information about total cost and effectiveness of fracture management and causes of adverse health outcomes in the hospitals. To overcome this information gap, the BFCC will develop and implement a transnational fracture registry with five hospitals from Estonia, Germany, Lithuania, Poland, and Sweden, respectively, providing evidence about fracture treatment in the clinical »real world« and reveal clinical needs as well as potentials for innovation.

The BFCC will publish two innovation reports. The Innovation Report No 1 deals with trends in the surgical treatment methods of proximal femur fractures. The Innovation Report No 2 based on results and findings from registry data analysis will identify innovation needs and potentials.

PHOTO: Shutterstock

1. INTRODUCTION

On 19th December 2017 the BFCC Transnational Fracture Registry Platform (TFRP) was launched by the University Medicine Greifswald (UMG) at production level. At the end of November 2018, a total number of 934 cases was entered and the registration process is still gaining speed.

Quality of the data entered into the registry is of utmost importance in order to correctly identify innovation potentials hidden in the diverse data. A validation process of the registry data is currently conducted to assess key quality measures. First results will be published during the Bone Innovation Summit in February 2019.

In addition to the primary objective of collecting data on fracture treatment in the Baltic Sea region, the BFCC establishes a transnational collaboration platform between hospitals and industry, which will be tested in three transnational pilots, with five hospitals and three companies involved. While the Common Minimum Dataset[1] defined during the first month of the project is the foundation for the data evaluation process, several additional parameters can be entered to be able to use the registry for more detailed data capture. The findings from the three pilots will also be published during the Bone Innovation Summit in February 2019.

Commonly, registries are just a sink of data for the clinicians entering the data. Scientific evaluations leading the published articles will eventually reflect some findings back to the clinicians. In this way, the treatment of future patients can be improved by providing evidence. Our approach to running a registry is to provide direct feedback to the participating hospitals, in addition to the in-depth scientific analysis of the data. An automatic statistical reporting system was implemented that creates reports for every site entering data on a monthly basis.

1.1. Addressing clinical needs

In addition to the analysis of the registered data, Innovation Dialogue Events have taken place at the partner sites. The basic assumption for the Innovation Dialogue Events is the ability of clinicians to name and describe problems related to fracture treatment procedures. Open discussions will lead to challenges for stakeholders addressing these issues in new products.

Some commonly addressed challenges are:

better instruments —
for material removal or as simple aiming devices

improved software solutions —
for surgical simulators, a fracture knowledge platform helping in evidence-based treatment decisions or for physical therapy

international scientific cooperation —
to improve fracture treatment strategies or to reduce the problem of infection.

1 See the interactive Dataset browser available on the project's homepage: https://bfcc-project.eu

2. FIRST ANALYSIS OF REGISTRY DATA

The evaluation of the registry dataset was conducted with the statistical programming software R [1] and the R-Markdown language made available in the software environment R-Studio [2] with the additional packages (reshape2, Version 1.4.3; dplyr, Version 0.76; tidyr, Version 0.8.1; ggplot2, Version 3.0.0; PairedData, Version 1.1.1; broman, Version 0.68–2; readxl, Version 1.1.0; readr, Version 1.1.1; scales, Version 1.0.0; eeptools, Version 1.2.0; plotly, Version 4.8.0; mondate, Version 0.10.01.02; operator.tools, Version 1.6.3; openssl, Version 1.1; RVAideMemoire, Version 0.9–70; FSA, Version 0.8.22) and their dependencies. The level of significance was set to $\alpha = 0.05$ throughout the analysis.

The dataset available, which was exported from the BFCC registry end of November 2018, contained 934 entries fulfilling the requirements of the Common Minimum Dataset[1] from four centers in Estonia, Germany, Lithuania and Poland. Checking the plausibility of the dates (date of birth, fracture, admission, discharge) reduced the number to 804 subjects. Also, the complication rate differed largely between the centers and was neglected for the evaluation.

2.1. Basic demographics of the study population

The total number of 804 subject contained 481 female and 323 male subjects (see Figure 1), which differed significantly ($p < 0.0024$; Fisher's Exact Test for Count Data) between the centers (see Figure 2). Pairwise post-hoc tests with p-value adjustment [3] confirmed a statistically significant difference between Estonia and Poland ($p < 0.0025$). The differences between the other centers were not statistically significance

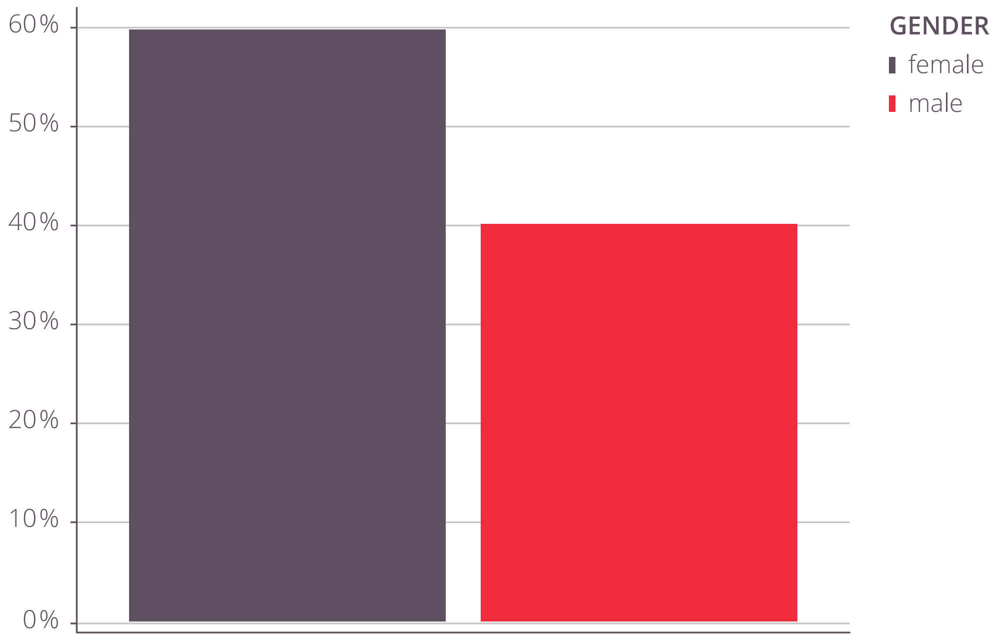


Figure 1: Gender distribution of the study population

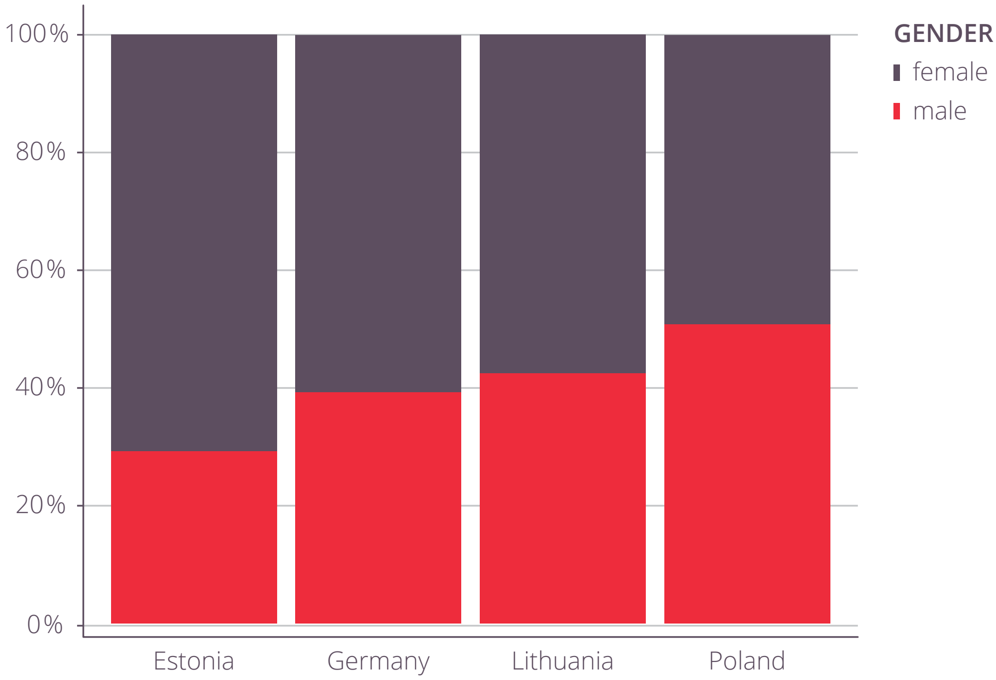


Figure 2: Gender distribution of the study population in the four countries

The range of age in the study population is between 18 and 104 years. The age differs significantly ($p < 0.001$; Kruskal-Wallis rank sum test) between the four countries and also the age distribution differs noticeably (see Figure 3).

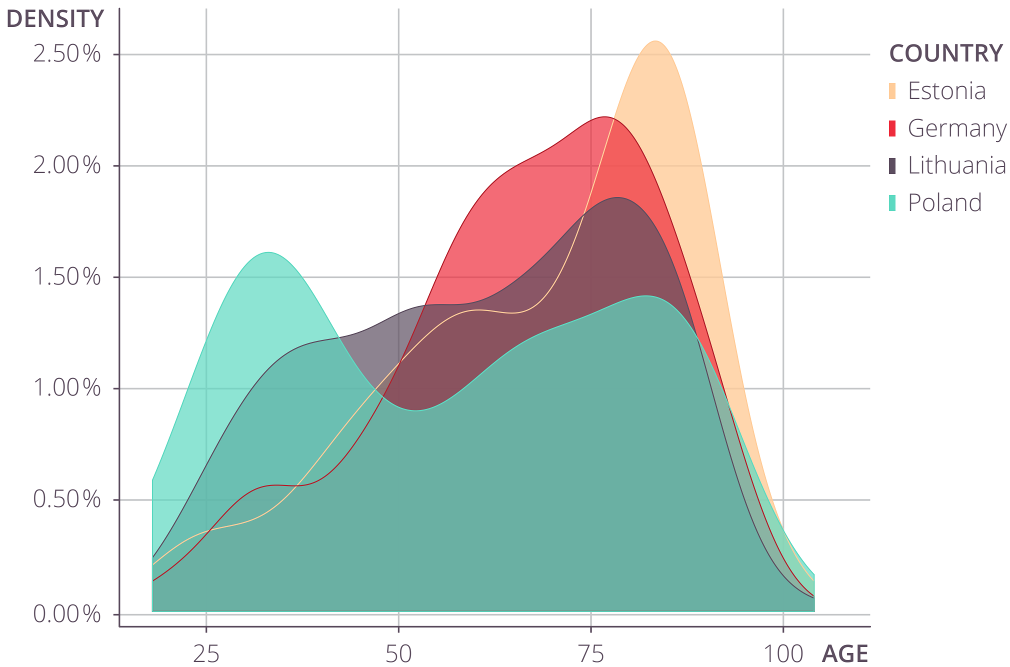


Figure 3: Age distribution

Especially interesting is the difference in age, when analyzed separately for male and female subjects (see Figure 4). As expected, the peak age of the male subjects is lower than for the female subjects ($p < 0.001$; Wilcoxon rank sum test with continuity correction), but also it differs significantly ($p < 0.001$; Kruskal-Wallis rank sum test) between the four countries. A correlation can be seen between the median age of the male subjects and the GDP (values in USD from 2017; source World Bank Group). Applying a regression model (see Figure 5) illustrates this correlation but statistically it is not significant ($p = 0.1571$; F-test on the regression model).

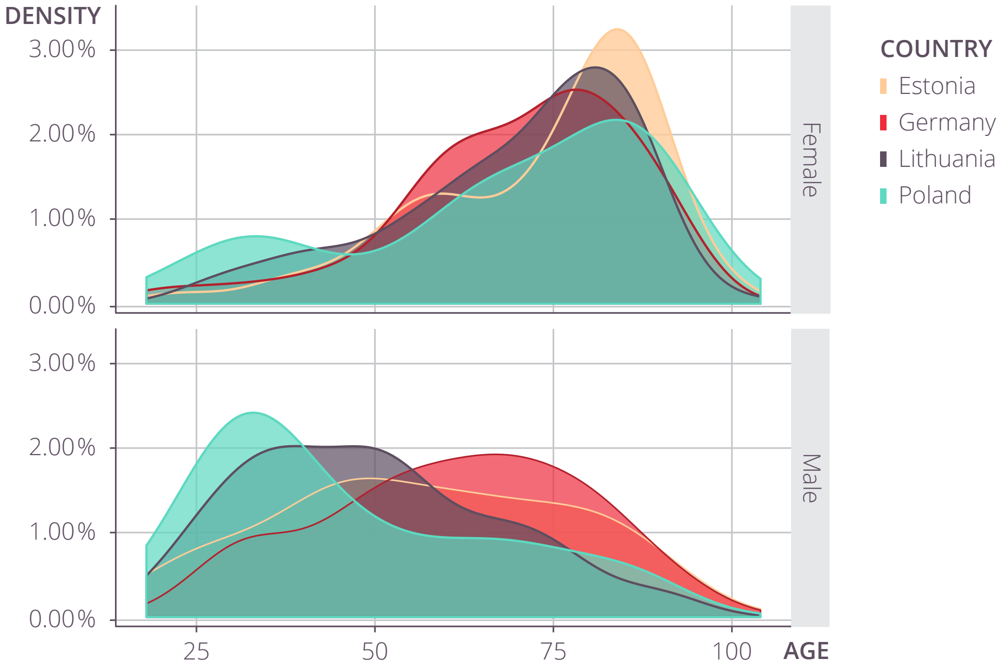


Figure 4: Age distribution for male and female subjects

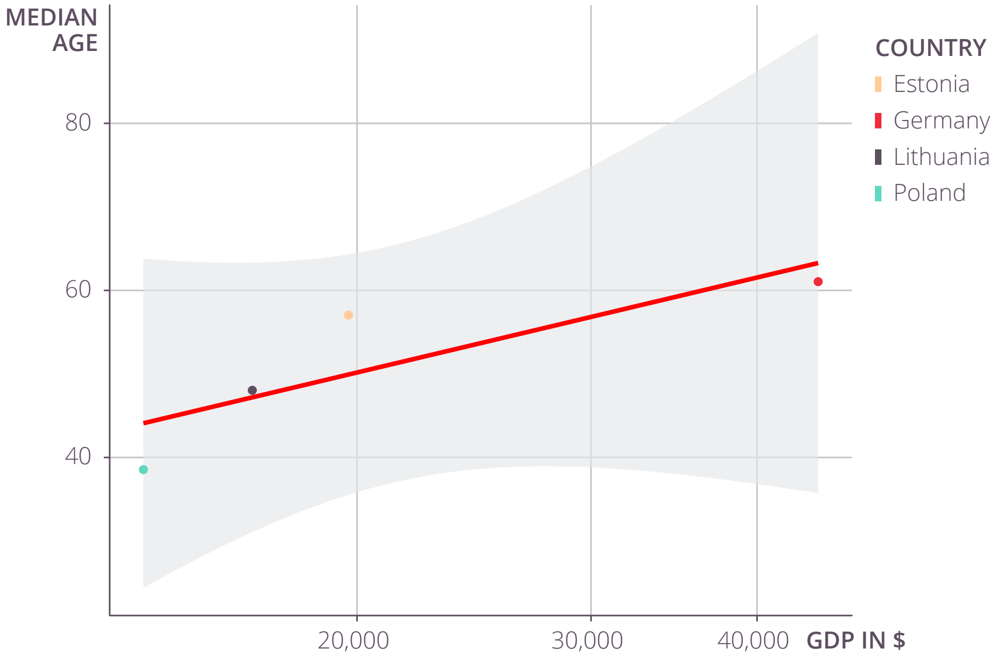


Figure 5: Median Age of the male subjects plotted over the GDP in $ (logarithmic scale; regression line in red)

2.2. Fractures registered

Analyzing the different fracture localizations, a peak can be seen in femoral fractures (see Figure 6 and Table 1).

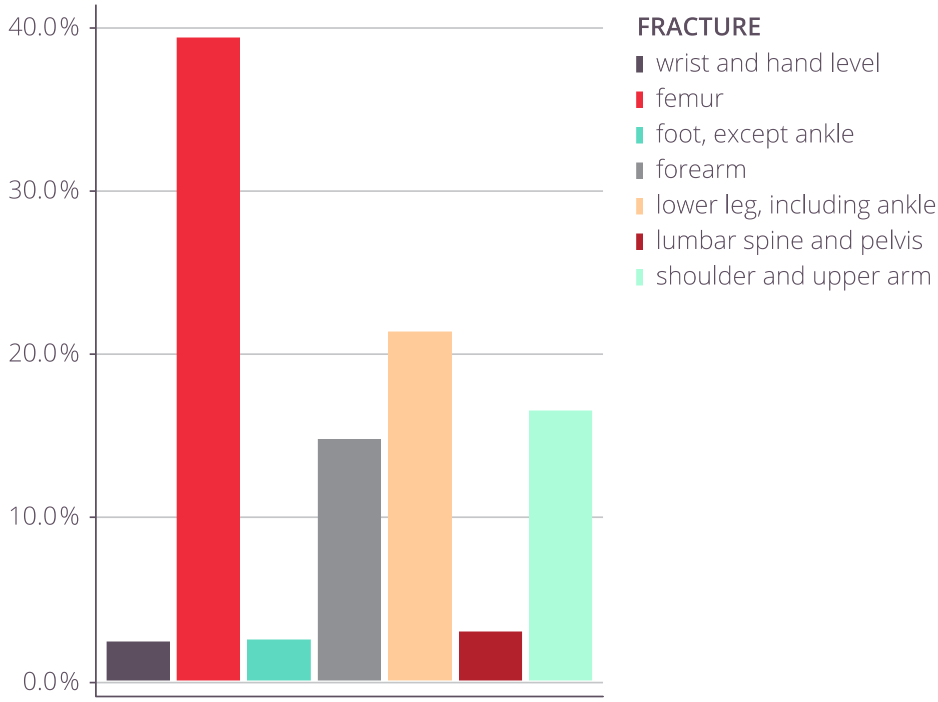


Figure 6: Distribution of the fracture localizations

FRACTURE	COUNT	PROPORTION
Fracture of femur	317	39.43%
Fracture of lower leg, including ankle	172	21.39%
Fracture of shoulder and upper arm	133	16.54%
Fracture of forearm	119	14.80%
Fracture of lumbar spine and pelvis	24	2.99%
Fracture of foot, except ankle	20	2.49%
Fracture at wrist and hand level	19	2.36%

Table 1: Fracture localizations

The distribution of the fracture localizations differs by gender ($p < 0.001$; Pearson's Chi-squared test; pooled over all countries) and country ($p < 0.001$; Pearson's Chi-squared test; pooled over both genders) (see Figure 7), but not for the distribution of fracture localization of the female subjects ($p = 0.2805$; Pearson's Chi-squared test).

Figure 7: Distribution of fracture localizations by gender and country

In total, 39 different types of fractures (using the ICD-classification) were present in the available data, with pertrochanteric fractures (n = 120; 14.9% of the study population) and femoral neck fractures (n = 110; 13.7% of the study population) being the most common (see Table 2).

FRACTURE	COUNT	PROPORTION
Pertrochanteric fracture	120	14.93%
Fracture of neck of femur	110	13.68%
Fracture of upper end of humerus	57	7.09%
Fracture of lower end of tibia	50	6.22%
Fracture of lower end of radius	43	5.35%
Fracture of lateral malleolus	33	4.10%
Fractures of other parts of lower leg	33	4.10%
Fracture of shaft of femur	32	3.98%
Fracture of clavicle	31	3.86%
Fracture of shaft of humerus	30	3.73%

Table 2: Top 10 fractures

2.3. Detailed analysis of pertrochanteric fracture

The total number 120 cases of pertrochanteric fractures contains 90 female subjects with a median age of 84 years (range: 37–99 years) and 30 male subjects with median age of 79.5 years (range: 30–96 years) (see Figure 8). The age differs significantly between genders (p = 0.0283; Wilcoxon rank sum test).

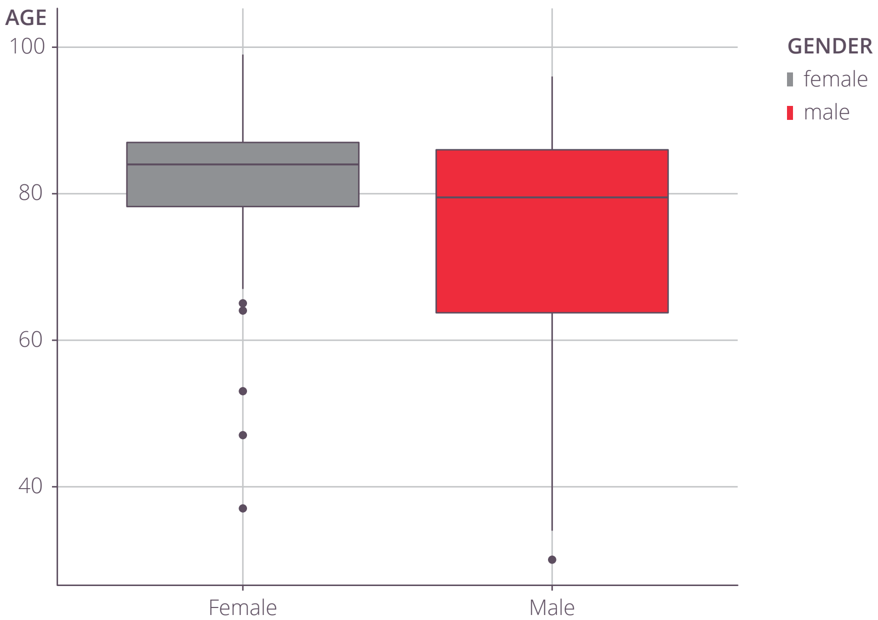


Figure 8: Age distribution for female and male subjects with pertrochanteric fracture

The duration of hospital stay is 8 days in median (8 days for female, 9 days for male subjects). This difference is not statistically significant different (p = 0.3982; Wilcoxon rank sum test). The duration of the hospital stay differs significantly (p < 0.0005; Kruskal-Wallis rank sum test) by the treatment methods or used implant (see Figure 9).

Pairwise post-hoc tests with Dunn's test [4] and p-value adjustment by Holm's method [5] reveal statistically significant differences in the hospital stay duration between:

intramedullary nail vs. proximal femoral nail	**p < 0.0018**
conservative vs. intramedullary nail	**p < 0.0035**
dynamic hip screw (DHS) vs. intramedullary nail	**p < 0.0227**

The median age of these four treatment groups is between 82 and 85.5 years and does not differ statistically significant (p = 0.752; Kruskal-Wallis rank sum test).

The frequency of being discharged home in comparison to being discharged elsewhere (summarizing being transferred to a nursing facility, a rehabilitation facility, a different hospital unit or to being deceased) of the subjects in the four groups was analyzed with a Pearson's Chi-squared test showing no statistically significant difference (p = 0.0897). The cross-table with the count data is given in Table 3. Even though 60% of the patients treated with the DHS implant can be discharged home in comparison to only 40% of the subjects treated with a different implant, this difference is statistically not significant (p = 0.1114; Pearson's Chi-squared test with Yates' continuity correction).

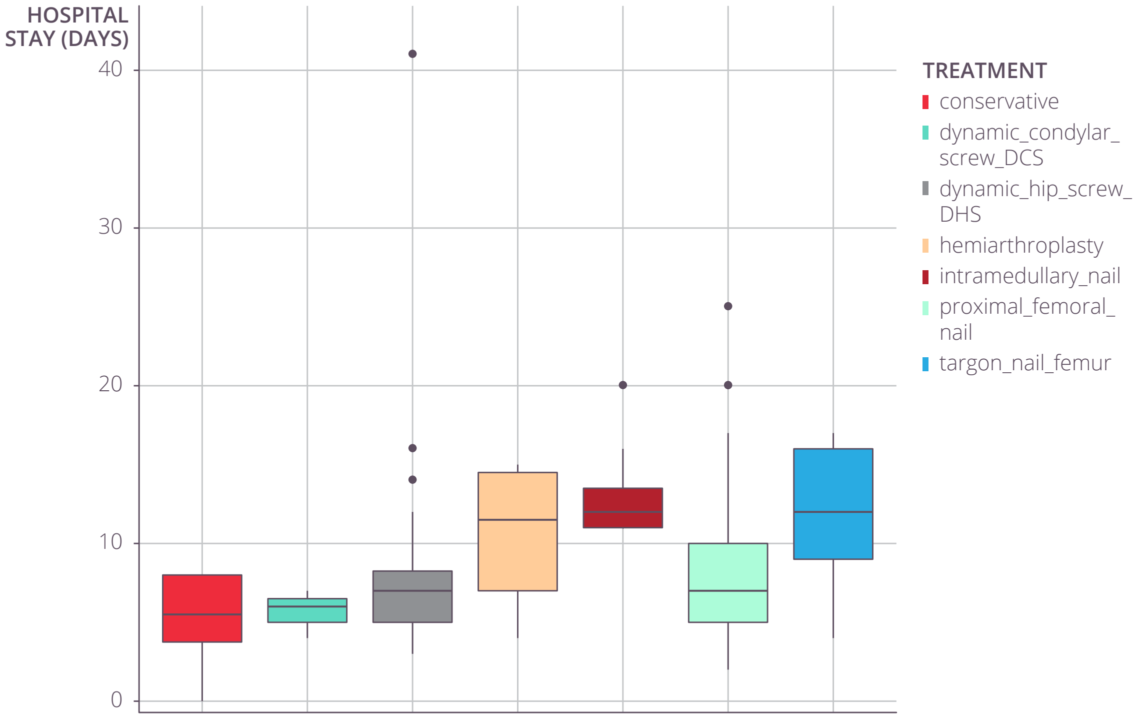


Figure 9: Hospital stay duration for the treatment of pertrochanteric fractures

TREATMENT	DISCHARGED HOME	DISCHARGED ELSEWHERE
Conservative	2	6
Dynamic hip screw (DHS)	12	8
Intramedullary nail	3	12
Proximal femoral nail	22	28

Table 3: Cross-table for pertrochanteric fracture — treatment vs. discharge

The ASA-score values of the operatively treated subjects (in the groups intramedullary nail, proximal femoral nail and dynamic hip screw [DHS]) were analyzed Pearson's Chi-squared test showing no statistically significant difference (p = 0.4062).

In summary, the registry data shows that the treatment of pertrochanteric fractures with an intermedullary nail seems to be associated with a prolonged hospital stay. The median duration of the hospital stay is 12 days in comparison to an overall median of 8 days.

2.4. Detailed analysis of femoral neck fractures

Analyzing the subjects with femoral neck fractures reveals 79 female subjects with a median age of 79 years (range: 37–96 years) and 31 male subjects with a mean age of 72 years (range: 38–92 years). (See Figure 10). The age differs significantly between genders ($p = 0.03711$; Wilcoxon rank sum test).

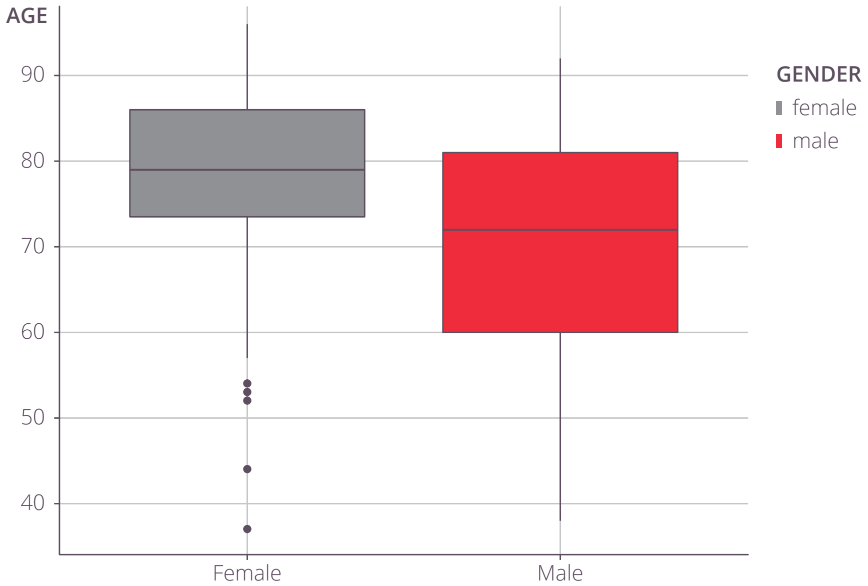


Figure 10: Age distribution for female and male subjects with femoral neck fractures

The duration of hospital stay is 7 days in median (for female and male subjects). No statistically significant difference was detected ($p = 0.789$; Wilcoxon rank sum test) in the distribution of the hospital stay duration between genders. The duration of the hospital stay differs significantly ($p = 0.0354$; Kruskal-Wallis rank sum test) by the treatment methods or used implant (see Figure 11).

Pairwise post-hoc tests with Dunn's test and p-value adjustment by Holm's method reveal a statistically significant difference in the hospital stay duration of subjects treated with cannulated screw vs. total endoprothesis ($p < 0.0194$).

The median age of these two treatment groups is 53 (cannulated screw) and 72 years (total endoprothesis) and does not differ statistically significant ($p = 0.0854$; Wilcoxon rank sum test).

The frequency of being discharged home in comparison to being discharged elsewhere (summarizing being transferred to a nursing facility, a rehabilitation facility, a different hospital unit or to being deceased) of the subjects in the two groups was analyzed with the Fisher's Exact Test showing no statistically significant difference ($p = 0.07331$). The cross-table with the count data is given in Table 4. Even though about 72% of the patients treated with cannulated screws can be discharged home in comparison to only about 28% of the subjects treated with a total endoprothesis, this difference is statistically not significant.

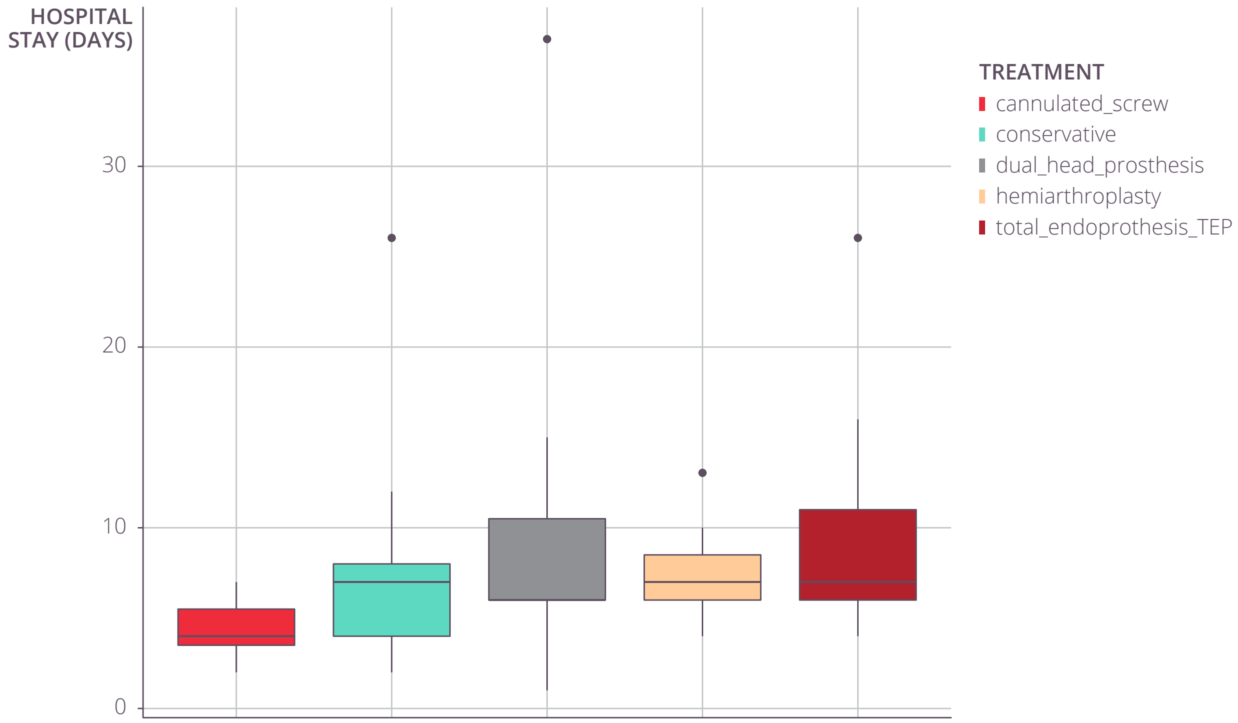


Figure 11: Hospital stay duration for the treatment of femoral neck fractures

TREATMENT	DISCHARGED HOME	DISCHARGED ELSEWHERE
Cannulated screw	5	2
Total endoprothesis	8	21

Table 4: Cross-table for femoral neck fracture — treatment vs. discharge

The ASA-score values of the subjects treated with cannulated screws or total endoprothesis was analyzed with a Pearson's Chi-squared test showing no statistically significant difference (p = 0.3997).

In summary, the registry data shows that the treatment of femoral neck fractures fractures with a total endoprothesis seems to be associated with a prolonged hospital stay compared to the treatment with cannulated screws. The median duration of the hospital stay is 7 days in comparison 4 days when treated with cannulated screws. Yet the sample numbers are already quite small (only 7 subjects for cannulated screw and 29 for total endoprothesis), the validity of the result should be re-evaluated after more subjects will have been registered.

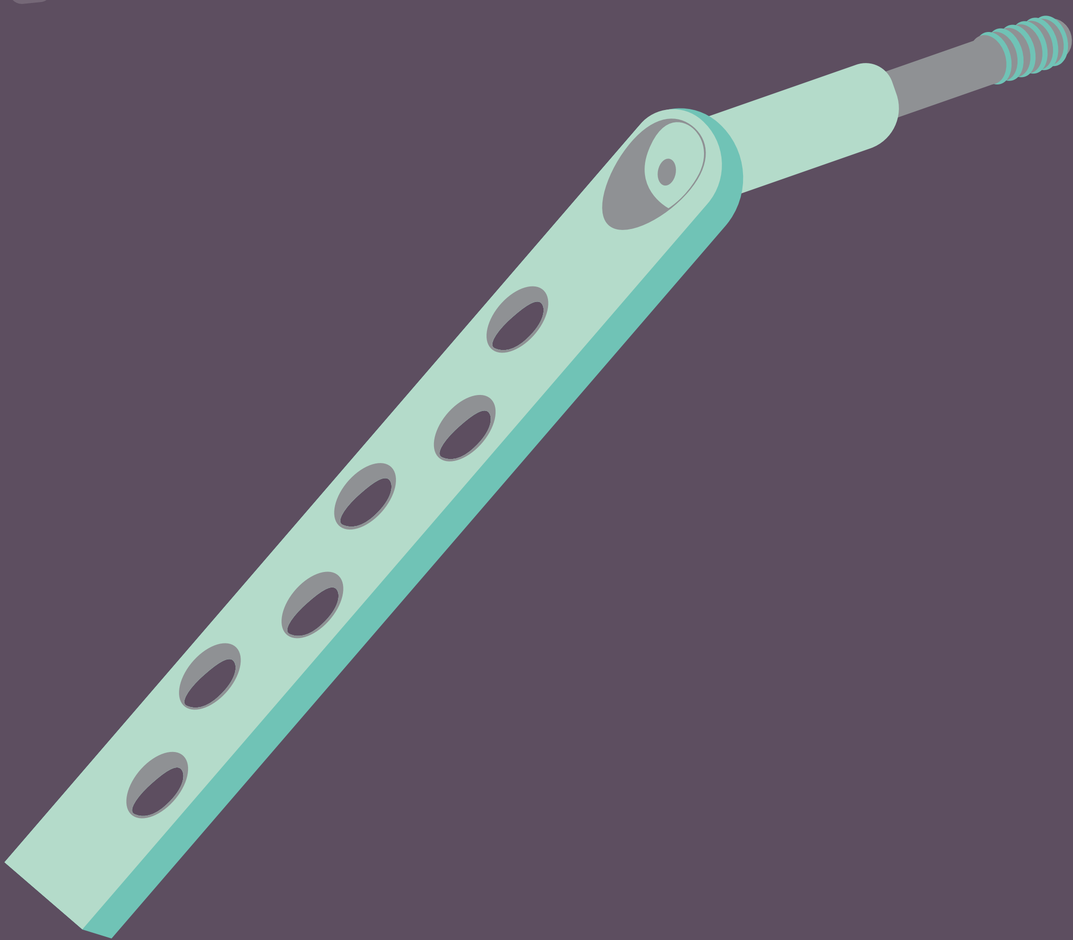
2.5. Summary of the first registry analysis

The evaluation of the registry data revealed innovation potential especially in the treatment of pertrochanteric fractures. Treatment with an intramedullary nail seem to be associated with a prolonged hospital stay, whereas the treatment with a Dynamic Hip Screw seems to be associated with a higher rate of patients being discharged home.

Comparing the registry data to the literature, congruent results can be found in age and gender ratio, e. g. [6–8]. For other parameters, as the recovery to previous functional level matching [9] as well as different results [6] are reported. The relatively low number of registered cases, considering the overall incidence of fractures, it is clear that a selectional bias will be present in the registry data.

Additionally, the implants used for treatment include a certain degree of fuzziness as the diverse implants are mapped to only 17 different implants in the BFCC's Common Minimal Dataset. Further insights might be feasible when the numbers of registered subjects will increase over time and the more specific implant identifier field of the full dataset can be utilized.

The relatively low sample numbers also require hand-crafted statistical analyses to be conceived and to be refined iteratively. Machine-learning approaches, as Random Forests [10] or Conditional Random Forests [11], still fail to correctly identify factors for worse or improved outcome.



3. AUTOMATED REGISTRY REPORTING

The automatic statistical reporting system is based on the statistical programming software R [1] and the R-Markdown language made available in the software environment R-Studio [2] with the additional packages (reshape2, Version 1.4.3; dplyr, Version 0.76; tidyr, Version 0.8.1; ggplot2, Version 3.0.0; PairedData, Version 1.1.1; broman, Version 0.68–2; readxl, Version 1.1.0; readr, Version 1.1.1; scales, Version 1.0.0; eeptools, Version 1.2.0; plotly, Version 4.8.0; mondate, Version 0.10.01.02; operator.tools, Version 1.6.3) and their dependencies.

The statistical report is fully defined in the R-Markdown file and is executed (knitted in R terminology) with parameters defining the data to be analyzed and the center for that the report is to be created. Another parameter is the required language of the report as it is fully localizable into different languages. The output is a html-file easily send via email, encrypted email or even instant messaging (using the highly secure Signal-messenger) to contact persons in the clinical sites.

The glue-logic for handling the imported registry data, executing the analysis and distributing the reports is implemented using Node-Red (Version 0.18), which is a flow-based programming system mainly used for Internet of Things applications. All of the software components run in a virtual machine hosting Ubuntu (Version 16.04.3 LTS).

3.1. Reported items

The automated statistical report created once per month contains basic information about:

- the number of patients included
- the number of patients included over time (see Figure 12)
- the distribution of gender
- the distribution of age (including a Wilcoxon-test — see Figure 13).

Number of validated cases in registry per month

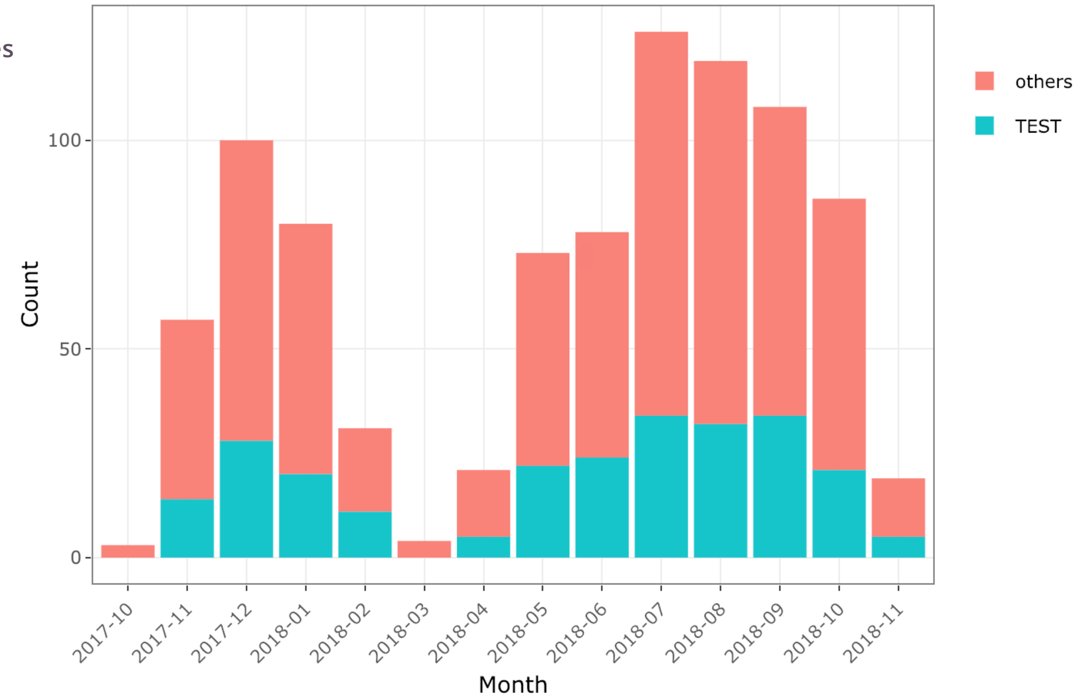
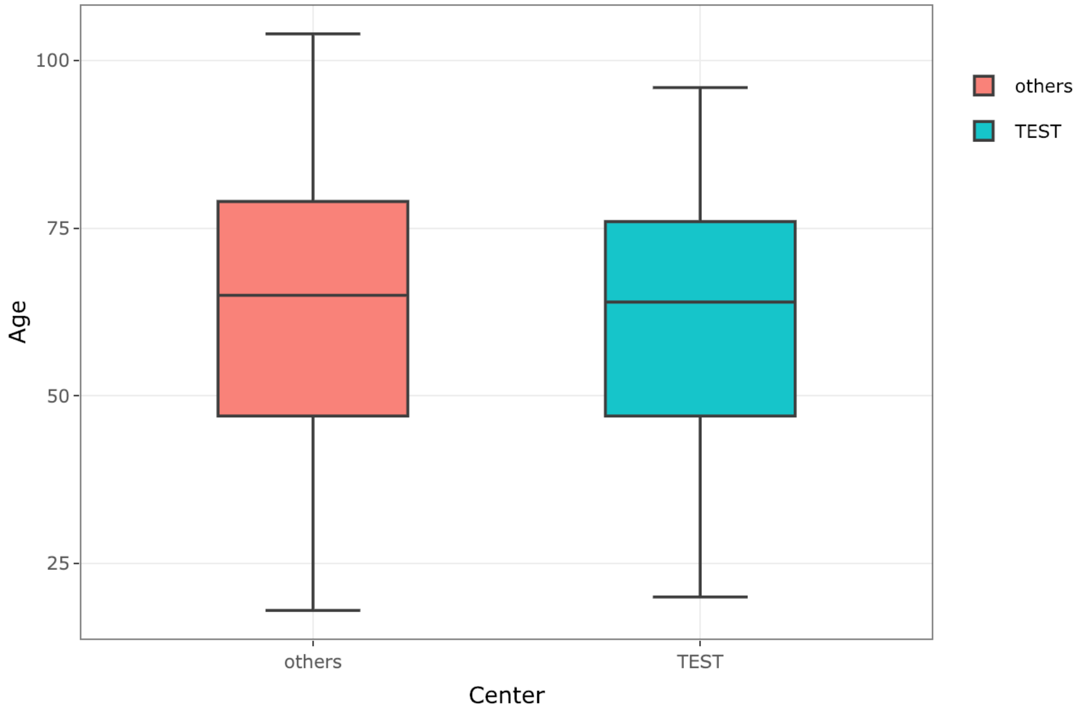


Figure 12: History of validated cases (screenshot from the report)



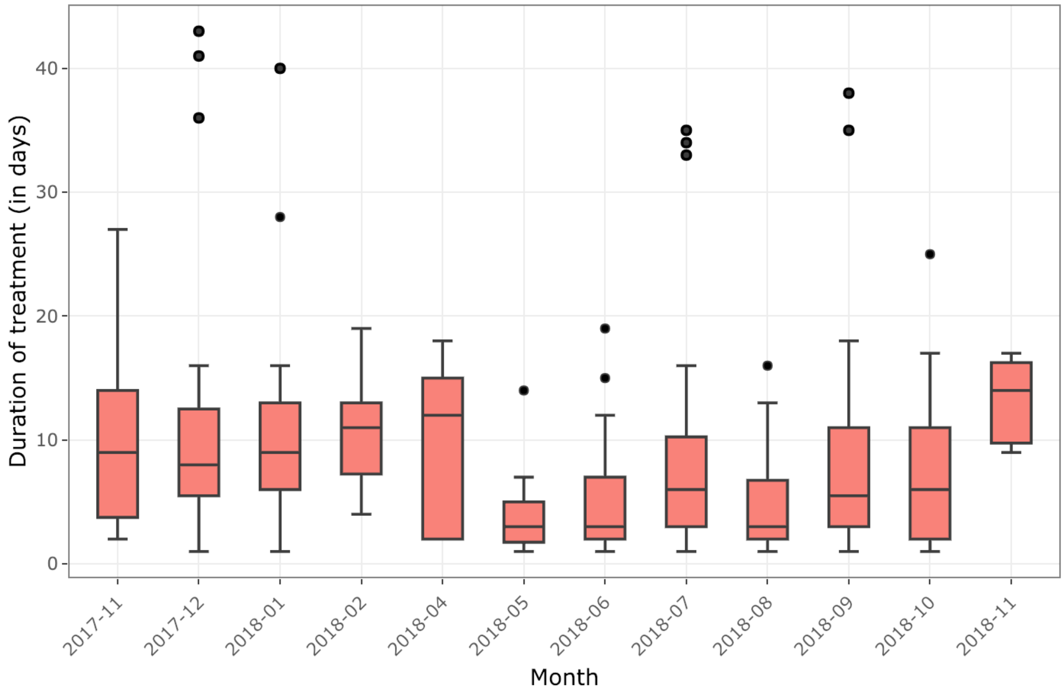
TEST Distribution of age (at time of fracture) (median): 64 years
others Distribution of age (at time of fracture) (median): 65 years

Distribution of age (at time of fracture) — Wilcoxon rank sum test with continuity correction: No significant difference (p = 0.4249)

Figure 13: Boxplot of the age distribution (screenshot from the report)

More specific information is given on:

- the complications rate (including a Fisher-test to compare the centers)
- the severity of complication
- the history of the complication rate (including a Fisher-test to assess a significant change of your center's complication rate in the last three months)
- the history of the complication rate (split into minor and severe complications)
- the different types of complications (as defined in the complication-classification sub-project)
- the duration of treatment (including a Wilcoxon-test to benchmark your center)
- the history of the duration of treatment (including a Wilcoxon-test to assess a significant change of your center's complication rate in the last three months — see Figure 14)
- the type of treatment (surgical or conservative)
- the implants used



Duration of treatment (median — last 3 months): 6.5 days
Duration of treatment (median — previous period): 6.0 days

Duration of treatment (last 3 months vs. previous period) —
Wilcoxon rank sum test with continuity correction: No significant difference (p = 0.8989)

Figure 14: History of the duration of treatment (screenshot from the report)

PHOTO: Adobe Stock

A sample report in different languages is available on the project's homepage.[2]

The plots given in the report are fully interactive: they are giving more information on mouse hover (see Figure 15) and are zoomable.

Figure 15: Detailed data on mouse hover (screenshot from the report)

2 https://bfcc-project.eu

4. PATIENT REPORTED OUTCOMES AFTER FRACTURE TREATMENT AT THE UKSH

During a three-month pilot phase from November 2017 until February 2018, 238 adult patients with less than a week-old fractures of the extremities, pelvis or the clavicle were asked for consent to be entered into the registry at the University Hospital in Lübeck, Germany. Their person identifying data was replaced by a pseudonym and saved in a trusted third-party server while medical data was entered on a separate system. Half a year post treatment a follow up letters with a concise questionnaire evaluating health status and possible complications was sent to each patient.

Response rate of the patient reported outcome questionnaire was 59.3%. Of those patients who answered 80.7% were satisfied with their treatment. 37.1% of patients reported to have some kind of complication.

Patient satisfaction and complications of fracture treatment were clearly related. The majority of patients that had reported to be satisfied with their treatment had no complications and vice versa, displayed in the following image:

Was the patient satisfied with his treatment?
ja = yes
nein = no

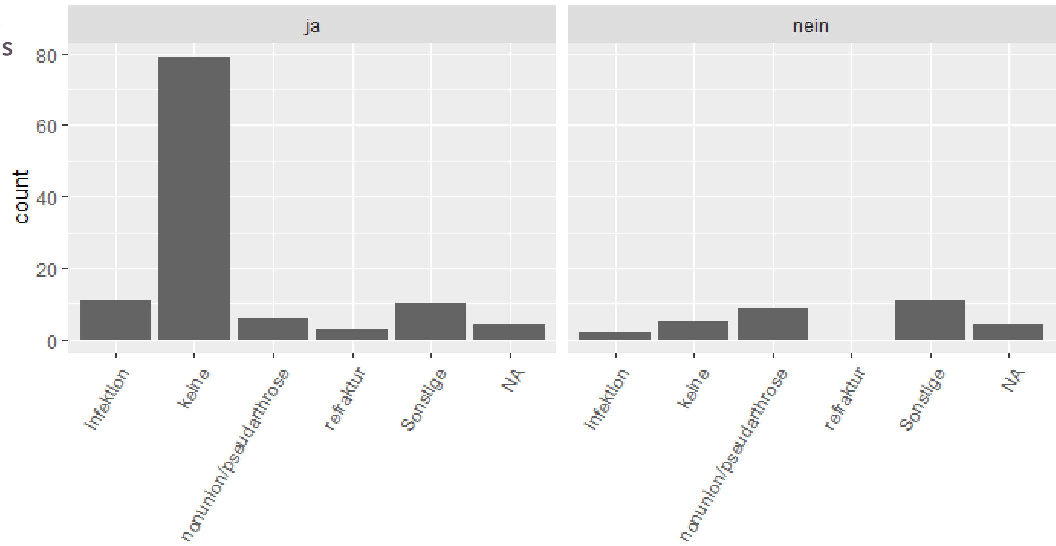
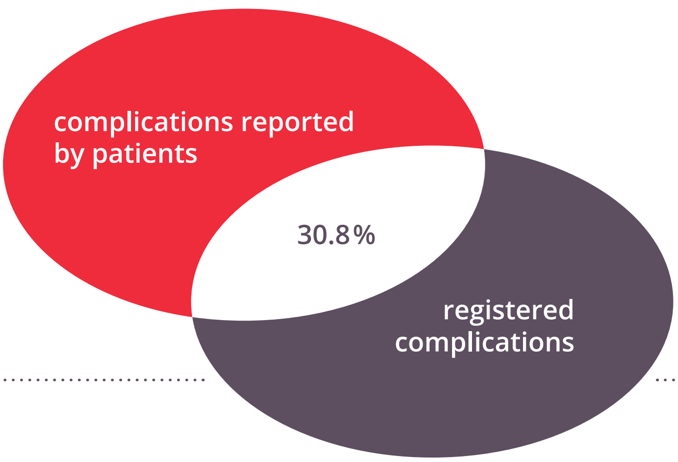


Figure 16: What kind of complication did the patient report to have had? keine = none, Sonstige = others (screenshot from the report)



16 patients that were registered having complications in the BFCC data base also reported themselves to have had a complication. This can be translated into an overlap of 30.8%.

Figure 17: Overlap of complications

5. REFERENCES

1 **R Core Team.** *R: A language and environment for statistical computing.* 2018.

2 **RStudio Team.** *RStudio: Integrated Development Environment for R.* 2016.

3 **Benjamini Y, Hochberg Y.** *Controlling the false discovery rate: a practical and powerful approach to multiple testing.* Journal of the royal statistical society. Series B, 1995: 289–300.

4 **Dunn OJ.** *Multiple comparisons using rank sums.* J Technometrics, 1964. 6(3): 241–252.

5 **Holm S.** *A simple sequentially rejective multiple test procedure.* Scandinavian journal of statistics, 1979: 65–70.

6 **Fairbanks M, *et al.*** *Epidemiology of Hip Fractures, a Retrospective Review.* 2016.

7 **Søgaard AJ, *et al.*** *Continued decline in hip fracture incidence in Norway: a NOREPOS study.* Osteoporosis International, 2016. 27(7): 2217–2222.

8 **Rosengren BE, *et al.*** *Recent hip fracture trends in Sweden and Denmark with age-period-cohort effects.* Osteoporosis International, 2017. 28(1): 139–149.

9 **Laires PA, *et al.*** *[Epidemiology of hip fractures and its social and economic impact. An update for 2014].* Acta reumatologica portuguesa, 2015. 40(3): 223–230.

10 **Breiman L.** *Random forests.* Machine learning, 2001. 45(1): 5–32.

11 **Hothorn T, Zeileis A.** *partykit: A modular toolkit for recursive partytioning in R.* The Journal of Machine Learning Research, 2015. 16(1): 3905–3909.

6. LIST OF FIGURES

7. LIST OF TABLES

PHOTO: Shutterstock

KEY FACTS

- Duration: 36 months (2016–2019)
- Total budget: about EUR 3.6 million
- Programme: Interreg Baltic Sea Region
- Fund: European Regional Development Fund
- Flagship project of the EU Baltic Sea Region strategy

PROJECT PARTNERS

- Life Science Nord Management GmbH (Germany; Lead Partner)
- Stryker Trauma GmbH (Germany)
- University Medical Center Schleswig-Holstein (Germany)
- University Medicine Greifswald (Germany)
- Sahlgrenska University Hospital (Sweden)
- ScanBalt fmba (Denmark)
- Lithuania University of Health Sciences (Lithuania)
- LifeScience Krakow Klaster (Poland)
- University Hospital in Krakow (Poland)
- University of Tartu (Estonia)
- Tartu Biotechnology Park (Estonia)
- Bone Index Finland Ltd. (Finland)
- BONESUPPORT AB (Sweden)

EU STRATEGY FOR THE BALTIC SEA REGION FLAGSHIP

www.bfcc-project.eu