PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A nonconcurrent cohort study to estimate the economic burden of infections following intramedullary nailing for a tibial shaft fracture in England
AUTHORS	Galvain, Thibaut; Chitnis, Abhishek; Paparouni, Konstantina; Tong, Cindy; Holy, Chantal; Giannoudis, Peter

VERSION 1 - REVIEW

REVIEWER	Carlos Magno Castelo Branco Fortaleza Botucatu School of Medicine São Paulo State University (UNESP) Brazil
REVIEW RETURNED	16-Feb-2020

GENERAL COMMENTS	The authors present a relevant nonconcurrent cohort study aimed at identifying direct costs of surgical site infections following intramedullary nailing for a tibial shaft fracture. Though their analysis was based on costs applied to the England healthcare system, the rationale of their analysis suggests that their data (with few variations) have global application. The most important limitation concerns the value of coded data for the diagnosis of surgical site infection. This approach has a varied and limited accurary, as concluded in a recent systematic review (BMJ Open. 2015;5(8):e008424). However, the authors correctly recognize the possibility of misclassification bias, and attempt to overcome it by rigorous methodological classification and inclusion/exclusion criteria. Other major limitation (the nonavailability of some data on costs) was tentatively overcome by searching published sources. Both the primary and secondary outcomes of interest were well defined and relevant. Methods applied for statistical analysis and adjustment of costs were appropriate. Results are presented in detail, but always clear and as concise as possible. Tables, figures and supplementary files are useful for understanding the rigorous steps taken by researchers. I have some minor recommendations that would improve the manuscript. 1. There is duplicate reference to the meta-analysis (reference no 6), so that the first mention (page 5, line 87) could be removed. 2. The term “retrospective cohort” is ambiguous, and some authors (e.g., Szklo & Nieto) insist that all cohorts are prospective (with data followed prospectively from exposure to outcome), even though studied event occurred in the past. Therefore, I suggest that both in abstract, introduction and methods the authors rather use “nonconcurrent cohort based on retrospectively collected data”. This

	would make it clear that the analysis is prospective, though data were collected from past events. 3. The very strict inclusion criteria aimed in providing a more "controlled" sample, it certainly narrowed the analysis for a subgroup more likely to have long-term follow-up and with few comorbidities. Though important for internal validity, this methodological choice limits the generalization of findings. Even though this is presented as a limitation (1) in the discussion, I think its importance requires further comments. 4. In Table 1, the demographic and clinical characteristics of patients with infections diagnosed in 1-year follow up are not presented (as the title suggests). Also, the Charlson comorbitiy index is analyzed as a continuous variable (with average and standard deviation), when it is a discrete variable better approached with median (range or quartiles) and nonparametric statistics. 5. Though beyond the scope of the present analysis, a study of secondary costs would be advisable. The authors comment on this aspect succinctly, in Page 16 lines 336-338. I think this should be included among limitations and discussed in more detail. 6. Among competing interests, the authors should explain whether their employees and funding corporations had any role in the study design, performance, analysis and in manuscript writing.

REVIEWER	Willem-Jan Metsemakers Department of Trauma Surgery University Hospitals Leuven, Belgium I'm a consultant for DepuySynthes (Johnson & Johnson Co)
REVIEW RETURNED	20-Apr-2020

GENERAL COMMENTS	The authors present a study that was aimed to determine the impact of infections on direct costs and healthcare resource use in England for patients undergoing intramedullary nailing (IMN) for tibial shaft fractures. Although overall it is a well conducted and interesting study I have some minor comments: Abstract Line 50: 805 patients met the inclusion criteria. Please change to Overall, 805 patients met the inclusion criteria. Introduction - The introduction is too long. I would shorten as follows: Lines 75 -85: Tibial shaft fractures are the most common type of long-bone fracture. They can be either closed fractures, where the skin remains intact, or open fractures (accounting for 25% of all tibial shaft fractures) where the skin is broken (1). Intramedullary nailing is a common surgical treatment for the fixation of the fractured bone: an intramedullary nail is inserted through the top of the tibia, into the inner cavity, and held in place with screws (1). Nailing allows preservation of the soft tissues surrounding the fracture site (1), and provides the greatest mechanical stability (2). In addition, as the nail is load-sharing rather than load-bearing, intramedullary nailing permits earlier weight-bearing on the fractured limb than other surgical treatments (3). Infection after intramedullary

	nailing is a potential complication, especially in severe open fractures, that can delay wound healing and fracture repair (2, 4-6). Please change to Tibial shaft fractures are the most common type of long-bone fracture. They can be either closed fractures, where the skin remains intact, or open fractures (accounting for 25% of all tibial shaft fractures) where the skin is broken (1). Intramedullary nailing is a common surgical treatment for this type of injury. Infection after intramedullary nailing is a serious complication, especially in open fractures, that can delay wound healing and fracture repair (2, 4-6). - Line 95 – 97: A Spanish study reported an infection rate of 2.7% in closed fractures compared with 19% in open fractures (10). Reference 10 focuses on pilon fractures, not on tibial shaft fractures which is the focus of this study. Please remove this reference (study) and add a recent study that discusses percentages related to tibial shaft fractures. Methods No comments Results No comments Discussion - Although this study does not focus on tibia fractures specifically, I would suggest the authors discuss it in their discussion as well (line 304 – 320): R.V. Thakore, S.E. Greenberg, H. Shi, et al. Surgical site infection in orthopedic trauma: a case-control study evaluating risk factors and cost. J Clin Orthop Trauma, 6 (2015), pp. 220-226 - An important limitation that should be better described in the limitation section of the discussion (line 321 - 331) is the arbitrary way infection was defined in this study. As mentioned well in the introduction, there is debate on the subclassification of infection. I would therefore add the following text to the limitation section: Surgical site infections were defined following the CDC criteria. Recently it became clear that the CDC definition for infection probably is not sufficient to define fracture-related infections. One important reason is the fact that the subdivision of infection into superficial and deep infection is arbitrary. However, the use of the CDC definition was standard during our study period (2003 – 2017). Add the following reference after: One important reason is the fact that the subdivision of infection into superficial and deep infection is arbitrary. Metsemakers WJ, Morgenstern M, McNally MA, et al. Fracture-related infection: A consensus on definition from an international expert group. Injury. 2018 Mar;49(3):505-510.

REVIEWER	Harm Hoekstra Dept of Trauma Surgery, University Hospitals Leuven, Belgium
REVIEW RETURNED	10-May-2020

GENERAL COMMENTS	Dear editor,

	I have read the manuscript entitled ‘A retrospective, longitudinal study of the healthcare resource utilisation and costs among patients with and without infection following intramedullary nailing for a tibial shaft fracture in England.’ with great interest, although the title should be catchier (shorter). Overall it is a very comprehensive and well written manuscript with a robust study design. The statistics are carried out sufficiently. Although the primary study findings are interesting and in-line with other studies, healthcare financing is country-specific, data and conclusions from this study cannot simply be compared linearly, without taking the differences in healthcare financing into account. The authors should address and explain England’ healthcare financing in more detail. The conclusion that infection prevention should curb the increasing costs is somewhat an open door. Due to a limited increase in total healthcare costs associated with infection and the relatively low infection rate, the impact on macro-scale is negligible. Can the infection rate go down much further? Is there actually a national wide protocol for the management of open fractures and are there hospital guidelines on length-of-stay in order to reduce variability? Please address this in the discussion. Furthermore, the definition of infection after fracture fixation has evolved over time. How was infection defined precisely? Please provide a reference. Regarding the inpatient total healthcare costs (and healthcare utilization), the authors fail to explain how they differentiate the costs related to the management of tibial shaft fracture from concomitant injury. The authors excluded patients with severe multiple injuries, hence the inclusion was not limited to mono trauma (i.e. tibial shaft fracture) apparently. Did the authors excluded the poly traumatised patients based on ISS? The attribution flow displayed in Figure 1 should clarified further on this. It remains unclear how the authors were able to generate the healthcare costs exclusively related to the tibial shaft fractures during the follow-up. The healthcare Costs may be biased by healthcare utilization due to other traumatic conditions during this period. Please comment on this. Nevertheless, we encourage the authors to address the issues above, revises the manuscript and resubmit it for peer review. Sincerely,

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Carlos Magno Castelo Branco Fortaleza Institution and Country:

Botucatu School of Medicine

São Paulo State University (UNESP)

Brazil

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below The authors present a relevant nonconcurrent cohort study aimed at identifying direct costs of surgical site infections following intramedullary nailing for a tibial shaft fracture. Though their analysis was based on costs applied to the England healthcare

system, the rationale of their analysis suggests that their data (with few variations) have global application. The most important limitation concerns the value of coded data for the diagnosis of surgical site infection. This approach has a varied and limited accurary, as concluded in a recent systematic review (BMJ Open. 2015;5(8):e008424). However, the authors correctly recognize the possibility of misclassification bias, and attempt to overcome it by rigorous methodological classification and inclusion/exclusion criteria. Other major limitation (the nonavailability of some data on costs) was tentatively overcome by searching published sources. Both the primary and secondary outcomes of interest were well defined and relevant. Methods applied for statistical analysis and adjustment of costs were appropriate. Results are presented in detail, but always clear and as concise as possible. Tables, figures and supplementary files are useful for understanding the rigorous steps taken by researchers.

I have some minor recommendations that would improve the manuscript.

1. There is duplicate reference to the meta-analysis (reference no 6), so that the first mention (page 5, line 87) could be removed.

We have removed the mention to this meta-analysis on line 87 and kept the one on line 99.

2. The term “retrospective cohort” is ambiguous, and some authors (e.g., Szklo & Nieto) insist that all cohorts are prospective (with data followed prospectively from exposure to outcome), even though studied event occurred in the past. Therefore, I suggest that both in abstract, introduction and methods the authors rather use “nonconcurrent cohort based on retrospectively collected data”. This would make it clear that the analysis is prospective, though data were collected from past events.

We have changed:

• The title line 1: we replaced “A retrospective, longitudinal study of the healthcare resource utilisation and costs among patients with and without infection following intramedullary nailing for a tibial shaft fracture in England” by “A nonconcurrent cohort study of the healthcare resource utilisation and costs among patients with and without infection following intramedullary nailing for a tibial shaft fracture in England”

• in the abstract line 34: we replaced ”A retrospective longitudinal (2 year) cohort study” by “Nonconcurrent cohort based on retrospectively collected data with 2 years follow-up.”

• In the intro line 111: we replace “The aim of this study was to determine the impact of infections…” by “The aim of this nonconcurrent cohort study was to determine the impact of infections…”

• in the methods line 116: we replaced “This was a retrospective longitudinal cohort study of patients in England who underwent intramedullary nailing for tibial shaft fracture (open or closed) followed-up for 2 years.” by “This was a nonconcurrent cohort study based on retrospectively collected data of patients in England who underwent intramedullary nailing for tibial shaft fracture (open or closed) and were followed-up for 2 years.”

3. The very strict inclusion criteria aimed in providing a more “controlled” sample, it certainly narrowed the analysis for a subgroup more likely to have long-term follow-up and with few comorbidities.

Though important for internal validity, this methodological choice limits the generalization of findings. Even though this is presented as a limitation (1) in the discussion, I think its importance requires further comments.

We added this precision on line 333 “thus excluding very severe patients with short life expectancy or with few comorbidities, limiting the generalizability of the findings to this subgroup.” Also we edited the figure1 to make it clearer.

4. In Table 1, the demographic and clinical characteristics of patients with infections diagnosed in 1-year follow up are not presented (as the title suggests). Also, the Charlson comorbitiy index is analyzed as a continuous variable (with average and standard deviation), when it is a discrete variable better approached with median (range or quartiles) and nonparametric statistics.

We have changed title of table 1 on line 211 from “Table 1. Patient demographic and clinical characteristics (index stay and 1-year analysis cohorts)” to “Table 1. Patient demographic and clinical characteristics at index” since 1 year follow up was presented in appendix 2.

We have changed presentation of Charlson score in table 1 to median and range, and used non parametric statistical test (Wilcoxon) to test differences.

5. Though beyond the scope of the present analysis, a study of secondary costs would be advisable. The authors comment on this aspect succinctly, in Page 16 lines 336-338. I think this should be included among limitations and discussed in more detail.

We added a limitation on line 330 as follows “7) economic assessment was limited to direct healthcare costs while infections could lead to permanent functional loss and potentially increase in secondary costs

(23).”

6. Among competing interests, the authors should explain whether their employees and funding corporations had any role in the study design, performance, analysis and in manuscript writing. We added a precision on line 364 :”The funding corporations could have affected the study design, analysis and manuscript writing; but authors owned final decisions.”

Reviewer: 2

Reviewer Name: Willem-Jan Metsemakers

Institution and Country:

Department of Trauma Surgery

University Hospitals Leuven, Belgium

Please state any competing interests or state ‘None declared’: I'm a consultant for DepuySynthes

(Johnson & Johnson Co)

Please leave your comments for the authors below The authors present a study that was aimed to determine the impact of infections on direct costs and healthcare resource use in England for patients undergoing intramedullary nailing (IMN) for tibial shaft fractures.

Although overall it is a well conducted and interesting study I have some minor comments:

Abstract

Line 50:

805 patients met the inclusion criteria.

Please change to

Overall, 805 patients met the inclusion criteria.

We changed the abstract line 805: from “805 patients met the inclusion criteria” to “Overall, 805 patients met the inclusion criteria”

Introduction

- The introduction is too long. I would shorten as follows:

Lines 75 -85:

Tibial shaft fractures are the most common type of long-bone fracture. They can be either closed fractures, where the skin remains intact, or open fractures (accounting for 25% of all tibial shaft fractures) where the skin is broken (1).

Intramedullary nailing is a common surgical treatment for the fixation of the fractured bone: an

intramedullary nail is inserted through the top of the tibia, into the inner cavity, and held in place with

screws (1). Nailing allows preservation of the soft tissues surrounding the fracture site (1), and provides the greatest mechanical stability (2). In addition, as the nail is load-sharing rather than load-bearing, intramedullary nailing permits earlier weight-bearing on the fractured limb than other surgical treatments

(3). Infection after intramedullary nailing is a potential complication, especially in severe open fractures,that can delay wound healing and fracture repair (2, 4-6).

Please change to

Tibial shaft fractures are the most common type of long-bone fracture. They can be either closed

fractures, where the skin remains intact, or open fractures (accounting for 25% of all tibial shaft fractures) where the skin is broken (1).

Intramedullary nailing is a common surgical treatment for this type of injury. Infection after intramedullary nailing is a serious complication, especially in open fractures, that can delay wound healing and fracture repair (2, 4-6).

We edited the introduction on line 75-85 from “Tibial shaft fractures are the most common type of longbone fracture. They can be either closed fractures, where the skin remains intact, or open fractures (accounting for 25% of all tibial shaft fractures) where the skin is broken (1).

Intramedullary nailing is a common surgical treatment for the fixation of the fractured bone: an

intramedullary nail is inserted through the top of the tibia, into the inner cavity, and held in place with

screws (1). Nailing allows preservation of the soft tissues surrounding the fracture site (1), and provides the greatest mechanical stability (2). In addition, as the nail is load-sharing rather than load-bearing, intramedullary nailing permits earlier weight-bearing on the fractured limb than other surgical treatments (3).

Infection after intramedullary nailing is a potential complication, especially in severe open fractures, that can delay wound healing and fracture repair (2, 4-6).”

- Line 95 – 97: A Spanish study reported an infection rate of 2.7% in closed fractures compared with 19% in open fractures (10).

Reference 10 focuses on pilon fractures, not on tibial shaft fractures which is the focus of this study.

Please remove this reference (study) and add a recent study that discusses percentages related to tibial shaft fractures.

We changed lines 89-91 from “A Spanish study reported an infection rate of 2.7% in closed fractures compared with 19% in open fractures (9).” To “A Belgian study reported an infection rate of 4.3% in patients with open or closed fractures, of which 1.4% were deep (9).”

Methods

No comments

Results

No comments

Discussion

- Although this study does not focus on tibia fractures specifically, I would suggest the authors discuss it in their discussion as well (line 304 – 320):

R.V. Thakore, S.E. Greenberg, H. Shi, et al. Surgical site infection in orthopedic trauma: a case-control study evaluating risk factors and cost. J Clin Orthop Trauma, 6 (2015), pp. 220-226

We added the following sentence on line 313-314 “Furthermore, a US-study found that surgical site infections nearly doubled inpatient costs to $109,000 in patients with isolated fractures (22).”

- An important limitation that should be better described in the limitation section of the discussion (line 321- 331) is the arbitrary way infection was defined in this study. As mentioned well in the introduction, there is debate on the subclassification of infection. I would therefore add the following text to the limitation section:

Surgical site infections were defined following the CDC criteria. Recently it became clear that the CDC definition for infection probably is not sufficient to define fracture-related infections. One important reason is the fact that the subdivision of infection into superficial and deep infection is arbitrary. However, the use of the CDC definition was standard during our study period (2003 – 2017).

Add the following reference after: One important reason is the fact that the subdivision of infection into superficial and deep infection is arbitrary. Metsemakers WJ, Morgenstern M, McNally MA, et al. Fracturerelated infection: A consensus on definition from an international expert group. Injury. 2018 Mar;49(3):505-510.

We added the following sentence on lines 319-323 “. Surgical site infections were defined following the CDC criteria (23, 24). Recently it became clear that the CDC definition for infection probably is not sufficient to define fracture-related infections. One important reason is the fact that the subdivision of infection into superficial and deep infection is arbitrary (25). However, the use of the CDC definition was standard during our study period (2003 – 2017)”

Reviewer: 3

Reviewer Name: Harm Hoekstra

Institution and Country: Dept of Trauma Surgery, University Hospitals Leuven, Belgium Please state any competing interests or state ‘None declared’: none

Please leave your comments for the authors below please find attached the comments

Dear editor,

I have read the manuscript entitled ‘A retrospective, longitudinal study of the healthcare resource

utilisation and costs among patients with and without infection following intramedullary nailing for a tibial shaft fracture in England.’ with great interest, although the title should be catchier (shorter).

We have changed the title to “A nonconcurrent cohort study to estimate the economic burden of infections following intramedullary nailing for a tibial shaft fracture in England”

Overall it is a very comprehensive and well written manuscript with a robust study design. The statistics are carried out sufficiently.

Although the primary study findings are interesting and in-line with other studies, healthcare financing is country-specific, data and conclusions from this study cannot simply be compared linearly, without taking the differences in healthcare financing into account. The authors should address and explain England’ healthcare financing in more detail.

We added the following precisions on line 143-149 : “Healthcare cost data were estimated based on the healthcare resource utilisation reported in CPRD/HES and the unit cost associated with each service from an NHS perspective. In England, NHS provides preventive medicine, primary care and hospital services to 88% of the citizens. Responsibility for publicly funded health care remains with the Secretary of State for Health, supported by the Department of Health (13). Hospitals are reimbursed by NHS according to the amount and type of activity that they perform using Healthcare Resource Groups (HRGs) (14).”

The conclusion that infection prevention should curb the increasing costs is somewhat an open door. Due to a limited increase in total healthcare costs associated with infection and the relatively low infection rate, the impact on macro-scale is negligible. Can the infection rate go down much further? Is there actually a national wide protocol for the management of open fractures and are there hospital guidelines on length-of stay in order to reduce variability? Please address this in the discussion.

We added the following precisions on lines 316-32 “Surgical site infections remain one of the most challenging complications in trauma surgery (23). Over the past decades, surgical site infection incidence has decreased, especially deep infections in patients with open tibial fractures (24). The question remained whether these rates could be decreased further. Still, no infections occurred in two studies in complex tibial fracture patients treated with antibiotic coated intramedullary tibia nails (25, 26). Based on consensus opinions, they may be a promising option for prevention of surgical site infections in open fractures or revision cases (27). Other approaches to prevent infections through local delivery of antibacterials were based on specialized biomaterials formulated as additives in bone void fillers such as bone cement or bacteriostatic bone substitute materials (23, 28, 29). Moreover, in order to prevent infections, open fractures should be managed according to the UK NICE guideline and the Open fracture BOAST (30, 31).

Furthermore, the definition of infection after fracture fixation has evolved over time. How was infection defined precisely? Please provide a reference.

We added the following sentence on lines 319-323 ". Surgical site infections were defined following the CDC criteria (23, 24). Recently it became clear that the CDC definition for infection probably is not sufficient to define fracture-related infections. One important reason is the fact that the subdivision of infection into superficial and deep infection is arbitrary (25). However, the use of the CDC definition was standard during our study period (2003 – 2017)"

Regarding the inpatient total healthcare costs (and healthcare utilization), the authors fail to explain how they differentiate the costs related to the management of tibial shaft fracture from concomitant injury.

The results have been adjusted for other comorbidities, including fracture type (open/closed), age, smoking status, index year, diabetes, COPD, inpatient waiting time for surgery and compartment syndrome using generalized linear models. That allowed to isolate as much as possible the effect of the infection on the outcomes. Although, this is limited by covariates/comorbidities that we selected and by those available in the data. We cannot control for all the potential confounders, thus this is a limitation. Therefore we added the following sentence in the limitations on line 331 "8) all potential confounders could not be adjusted for, limiting the association between increased healthcare resource utilizations and costs with surgical site infections." We also changed the sentence on line 181 from "Generalised Linear Models were used to adjust for confounding." To "Generalised Linear Models were used to adjust for confounding, to isolate the association between surgical site infection and the outcomes.

The authors excluded patients with severe multiple injuries, hence the inclusion was not limited to mono trauma (i.e. tibial shaft fracture) apparently. Did the authors excluded the poly traumatised patients based on ISS? The attribution flow displayed in Figure 1 should clarified further on this.

Patients were excluded from the analysis if they had a record of multiple injuries (based on ICD-10 codes cf. appendix 1, not ISS) in the prior year from the tibial fracture as said in Figure 1, but not at the same time as the tibial fracture. Exclusion in the prior year were applied to prevent looking a patients that already had a similar event in past. For clarity we refined figure 1 and added a precision that "in the 12-month pre-index period" was in fact "in the 12-month pre-index period (excluding index)". Our study is on patients with isolated or not tibial fractures. We edited the sentence on line 123-126 from "The study population included adults (aged ≥18 years) who were diagnosed with a tibial shaft fracture (ICD-10 code: S82.2) between May 2003 and June 2017 and who subsequently underwent intramedullary nailing within 30 days of diagnosis. Inclusion and exclusion criteria and patient attrition flow are depicted in Figure 1." To "The study population included adults (aged ≥18 years) who were diagnosed with an isolated (or not) tibial shaft fracture (ICD-10 code: S82.2) between May 2003 and June 2017 and who subsequently underwent intramedullary nailing within 30 days of diagnosis. Inclusion and exclusion criteria and patient attrition flow are depicted in Figure 1."

We could not narrow down more our cohort as it would have dramatically reduced our sample size by roughly half.

It remains unclear how the authors were able to generate the healthcare costs exclusively related to the tibial shaft fractures during the follow-up. The healthcare Costs may be biased by healthcare utilization due to other traumatic conditions during this period. Please comment on this.

The costs in the follow up were not directly related to the tibial shaft fractures, but any costs. The objective of this work was not to evaluate the costs of tibial shaft fractures by themselves, which would have required a different methodology. But it was to evaluate the costs of the infections associated with the tibial fracture, or "on top" of the tibial fractures. Therefore, the most interesting part here is not the total costs for each group but the difference between groups that we can associate with infections.

Nevertheless, we encourage the authors to address the issues above, revises the manuscript and resubmit it for peer review.

Sincerely,

VERSION 2 – REVIEW

REVIEWER	Carlos Magno Castelo Branco Fortaleza Department of Infectious Diseases Botucatu School of Medicine São Paulo State Unversity (UNESP) Brazil
REVIEW RETURNED	18-Jun-2020

GENERAL COMMENTS	The authors responded to revirewers' comments appropriately and changed the manuscript accordingly.ns. Not only the revised text is improved in terms of readability, but limitations of inferences due to the methodological choices of to the the specific characteristics of NHS were stressed.

REVIEWER	Harm Hoekstra Department of Trauma Surgery, University Hospitals Leuven
REVIEW RETURNED	15-Jun-2020

GENERAL COMMENTS	All comments have been addressed sufficiently