Is There a Role for CT Pan-Scans in the Initial Workup of Fragility Fracture Patients?

Eric Lepkowsky, MD1, Trevor Simcox, MD2, Hunter Rogoff, BS1, Omid Barzideh, MD2, and Shahidul Islam, PHD, MPH2

Abstract
Introduction: Computed tomography (CT) pan-scans have become increasingly commonplace as part of the initial diagnostic workup for patients sustaining traumatic injuries. They have proven effective in improving diagnostic accuracy in those with high-energy mechanisms of injury. However, the utility of pan-scans in the geriatric population sustaining low-energy traumatic injuries remains unproven. Methods: A retrospective review was conducted of patients who sustained a fragility fracture at a level-I trauma center over a 15-month period. Radiologist interpretations of any CT pan-scans were reviewed for acute findings, and charts were reviewed for resulting changes in orthopedic and nonorthopedic management. Additionally, mechanism of injury, definitive management, time to surgery, length of stay, level of care at discharge, and demographic data were compared against similar patients who did not receive a pan-scan. Results: Of the 109 patients who underwent a CT pan-scan, 1 (0.92%) had a change in orthopedic treatment. Twelve (11.01%) patients had changes to their nonorthopedic management. In addition, 14 other patients had one or more consultations obtained based on pan-scan results that did not result in any change in management. Discussion: This study found that only 1 of the included patients had a change in orthopedic management and 12 had a change in nonorthopedic management, despite over half of the study population being found to have additional findings. Furthermore, patients who underwent a pan-scan did not have expedited surgical intervention or earlier discharges compared to those who were not pan-scanned. Conclusion: This study demonstrates whole-body CT imaging provides little benefit in geriatric patients who sustain fragility fractures and should be utilized judiciously and in a targeted fashion instead of as a routine part of trauma surgery or emergency department protocol in this patient population. Level of Evidence: Level III Retrospective Study.

Keywords
fragility fractures, geriatric trauma, osteoporosis, trauma surgery, systems of care

Submitted December 13, 2019. Accepted March 09, 2020.

Introduction
As the geriatric patient population continues to grow, it has become increasingly important for orthopedists to understand how the treatment of the elderly individuals differs from that of younger patients. The population of people older than 65 is expected to double in the United States by 2060.1,2 Health-care cost in the United States from traumatic injury in this population is estimated to cost more than $34 billion annually, and the cost is only predicted to increase as the population ages.3,4 Consequently, fragility fractures, which are fractures caused by a mechanism that would normally be insufficient to break otherwise healthy bone, will comprise an even larger portion of fractures that are managed by orthopedists.1-9 More attention must be paid to traumatic injuries in geriatric patients, as elderly patients are frail, have diminished physiological reserve, and are at increased risk of morbidity and mortality.3-7,10,11 One area of interest is the utility of performing a whole-body computed tomography (CT) scan, often referred to as a pan-scan, in the setting of lower energy mechanisms of injury.12-15 The benefits of these pan-scans include minimizing missed diagnoses of soft tissue injuries, decreased time needed for workup, and lesser intensive care requirements.3,11,12,14,16-19

1 Department of Orthopedic Surgery, Stony Brook University, Stony Brook, NY, USA
2 Department of Orthopedic Surgery, NYU Winthrop Hospital, Mineola, NY, USA

Corresponding Author:
Eric Lepkowsky, Department of Orthopedic Surgery, Stony Brook University, HSC 18-030, Stony Brook, NY 11794, USA.
Email: eric.lepkowsky@stonybrookmedicine.edu
Pan-scans have proven to be effective and, in recent years, have become a commonplace part of the initial workup for the general trauma population. However, there has been a dearth of research focusing on the utility of obtaining a pan-scan in the geriatric trauma population with isolated orthopedic injuries.

The evidence regarding the utility of CT pan-scans in the geriatric trauma population is mixed, with some studies finding benefit while others failing to show significant impact on outcomes. Increased utilization of pan-scans has led to a commensurate increase in incidental findings while portending little to no impact on final treatment or outcomes in this patient population. Ultimately, this represents an unnecessary health-care cost and may lead to a potential delay in definitive management of their presenting complaint. Protocol-based use of pan-scans have failed to show any improvement in patient mortality. Several studies have shown some benefit, such as preventing under triage, decreased time to diagnosis, and improved diagnostic accuracy. However, these studies address the general trauma population or any trauma occurring in the geriatric population. To our knowledge, no study has directly addressed orthopedic management in patients who have sustained fragility fractures and are subject to this diagnostic strategy. This study seeks to determine how CT pan-scans impact the total care of the elderly trauma patient who has sustained a fragility fracture.

Methods

We performed a retrospective analysis of all patients admitted with fragility fractures between October 2017 and January 2019 following presentation to the emergency department (ED) at our facility. Our institution is a level-1 trauma center that serves as a community hospital for a major metropolitan area and treats more than 300 patients who sustain a fragility fracture every year. Per hospital protocol, these patients undergo an initial workup by the trauma surgery (TS) or ED teams and the fragility fracture service (FFS) is then consulted if an orthopedic injury is found. This population was reviewed for the purposes of this study. Inclusion criteria consisted of patients older than 50 years of age who sustained a fracture via a low-energy mechanism. Low-energy mechanisms were defined as a fall <1 meter of height off the ground. Age over 50 was chosen because at this age osteoporosis becomes an increasing concern, while the majority of fractures in this demographic occur due to a ground-level fall.

Patients indicated for inclusion in the study were assessed with regard to orthopedic diagnosis, mechanism of injury, orthopedic operative management, time to surgery (TTS), hospital length of stay (LOS), level of care at discharge, and TS or ED team workup with a CT pan-scan. Patients who underwent a CT pan-scan had the indication(s), the findings, and any subsequent consultations or changes in management reviewed. Background demographics including age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) score, and Charlson Comorbidity Index (CCI) were also noted. CT pan-scans were ordered at the discretion of either a TS or ED attending physician. A CT pan-scan was defined as CT imaging of the head, cervical spine, chest, abdomen, and pelvis. Radiologist interpretations of the CT pan-scan were reviewed for acute findings. New findings not previously demonstrated in the medical record or any acute exacerbations of a previously diagnosed condition were considered to be an acute finding. All associated clinical documentation was reviewed for any changes in orthopedic and nonorthopedic management that occurred because of findings discovered by the pan-scan. Clinical documentation was also reviewed to determine whether pan-scan findings correlated with patient’s presenting history and physical examination. Injuries of the spine were not considered orthopedic injuries for the purposes of this study.

Patients were grouped based on whether or not they underwent a pan-scan at the initial TS or ED workup. Groups were then compared regarding demographic characteristics, orthopedic diagnosis, mechanism of injury, TTS, LOS, and discharge level of care. Demographic characteristics were described using median (interquartile range) and frequency (percentage) where appropriate. Continuous variables were assessed for normality using Kolmogorov-Smirnov test, histograms, and probability plots. Based on the distribution of the data, Wilcoxon rank-sum test was used to compare continuous variables and Fisher exact test for categorical variables. A result was considered statistically significant at the P < .05 level. All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina).

Results

A total of 433 patients were indicated for review during the study period. Of those screened, 109 (25.17%) received pan-scans. Demographic data was compared between patients who received a pan-scan and those who did not (Table 1). Patients with an initial trauma CT pan-scan were more likely to have a higher ASA score. All other demographic variables were comparable.

In all, 114 orthopedic injuries were sustained by the 109 patients who underwent whole-body CT imaging. Figure 1A demonstrates the different orthopedic diagnoses in these patients. The most common of these were fractures of the peritrochanteric region (40.37%), fractures of the femoral neck (16.51%), and pelvic ring fractures (10.09%). With regard to mechanism of injury, 102 were due to mechanical ground-level falls. Of the remainder, 3 were falls of elevated height less than 1 meter, 2 were syncopal ground-level falls, and 1 was atraumatic in nature. In all, 91 (83.49%) patients did not have a documented indication for why a pan-scan was obtained (Table 2). Additionally, 68 (62.39%) of the patients who underwent a pan-scan required eventual surgical intervention for their orthopedic diagnosis.

Fifty-eight (53.21%) patients who underwent whole-body CT imaging had one or more findings that had not been previously demonstrated (Figure 1B). These most common findings


demonstrates the different orthopedic diagnoses in these patients. The most common of these were fractures of the peritrochanteric region (40.37%), fractures of the femoral neck (16.51%), and pelvic ring fractures (10.09%). With regard to mechanism of injury, 102 were due to mechanical ground-level falls. Of the remainder, 3 were falls of elevated height less than 1 meter, 2 were syncopal ground-level falls, and 1 was atraumatic in nature. In all, 91 (83.49%) patients did not have a documented indication for why a pan-scan was obtained (Table 2). Additionally, 68 (62.39%) of the patients who underwent a pan-scan required eventual surgical intervention for their orthopedic diagnosis.

Fifty-eight (53.21%) patients who underwent whole-body CT imaging had one or more findings that had not been previously demonstrated (Figure 1B). These most common findings
were thoracolumbar spine pathology (30.49%), chest wall or lung pathology (19.51%), and cranial or intracranial pathology (12.30%). Examples of these findings include vertebral compression fractures, rib fractures, and subdural hemorrhages, respectively. Patients who underwent a pan-scan were also found to have no differences in TTS and LOS when compared to those who did not. In addition, there was only a weak statistical correlation with discharge level of care when comparing patients who did and did not undergo whole-body CT imaging (Table 3).

As for orthopedic management, 1 (0.92%) patient had a change in treatment following pan-scan. There was a concern in this patient for a femoral neck fracture based on X-ray and initial physical examination. The radiology attending impression of the subsequent CT pan-scan raised doubt about an acute fracture but was worrisome for a lytic lesion of the femur. This patient underwent magnetic resonance imaging (MRI) scan that demonstrated no fractures or lytic lesion. Patient’s management plan was thusly changed from operative to nonoperative. There was no other impact found on the remaining patients’ orthopedic management based on CT pan-scan results.

Similar assessment was performed for changes to nonorthopedic management of these patients. Twelve (11.01%) patients had changes to their nonorthopedic management, 5 of them required an increased level of monitoring, 5 required nonoperative bracing of spinal fractures, and 2 required invasive intervention. In addition, 14 other patients had one or more consultations obtained based on pan-scan results that did not result in any change in management. Of the 12 patients who had changes in their nonorthopedic management, 10 had either a presenting history or suggestive prescan physical examination finding that directly correlated with their additional findings on pan-scan. Of the 2 patients who did not have correlating presentations, 1 required embolization of a pelvic hemorrhage by interventional radiology and the other required a thoracolumbar orthosis for vertebral compression fracture.

Table 1. Demographic Characteristics.

| Factors                  | Pan-Scan Performed, N = 109 | Pan-Scan Not Performed, N = 109 | P Valuea |
|-------------------------|-----------------------------|---------------------------------|----------|
| Age, median (IQR)       | 87 (81-89)                  | 86 (78-90)                      | .102     |
| BMI, median (IQR)       | 24.5 (22.9-28.4)            | 24.4 (21.6-28.3)                | .338     |
| Gender, n (%)           |                             |                                 | .229     |
| Male                    | 19 (17.4)                   | 76 (23.5)                       |          |
| Female                  | 90 (82.6)                   | 248 (76.5)                      |          |
| Charlson score, median (IQR) | 5 (4-6)                    | 5 (4-6)                         | .026     |
| ASA score, n (%)        |                             |                                 | .005     |
| 1                       | 0 (0)                       | 2 (0.8)                         |          |
| 2                       | 5 (6.8)                     | 50 (19.1)                       |          |
| 3                       | 44 (59.4)                   | 162 (61.8)                      |          |
| 4                       | 25 (33.8)                   | 48 (18.3)                       |          |

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; IQR, interquartile range.

aP values are from Wilcox rank-sum test for continuous variables and Fisher exact test for categorical numbers.

Discussion

Whole-body CT imaging has been increasingly used in the setting of acute trauma in the United States and has become protocoll as part of the initial general trauma workup at many institutions.12-15 However, the benefits of this practice in elderly patients with low-energy trauma are unclear. To our knowledge, this is the first study to assess the impact CT pan-scans have on the management of fragility fracture patients. Ours is the first study to seek to determine whether routine CT pan-scans should remain part of TS and ED protocols.

This study demonstrated that of the 109 patients who underwent CT scans, only 1 patient had a change in orthopedic management and 12 had a change in nonorthopedic management, despite over half of the study population being found to have additional acute findings. Furthermore, patients who underwent a pan-scan did not have significantly different TTS or LOS compared to those who did not, indicating that their
Table 2. Indications for Pan-Scans.

| Indication for Pan-Scan                        | Number of Patients |
|-----------------------------------------------|--------------------|
| No indication documented                      | 91 (83.4%)         |
| Loss of consciousness/altered mental status   | 10 (9.17%)         |
| Metastatic workup                              | 3 (2.78%)          |
| Hypotension                                    | 2 (1.83%)          |
| History of cardiopulmonary disease            | 2 (1.83%)          |
| Sepsis workup                                  | 1 (0.97%)          |

Table 3. Bivariate Comparisons of Outcomes.

| Outcomes                        | Pan-Scan Performed, N = 109 | Pan-Scan Not Performed, N = 109 | P Valuea |
|---------------------------------|-----------------------------|---------------------------------|----------|
| Length of stay, days, median (IQR) | 5 (3-7)                     | 5 (3-6)                         | .339     |
| Disposition, n (%)              |                             |                                 | .044     |
| Home                            | 17 (15.6)                   | 66 (21.4)                       |          |
| Rehab                           | 85 (78.0)                   | 236 (76.6)                      |          |
| Expired/hospice/palliative      | 7 (6.4)                     | 6 (2.0)                         |          |
| Time to surgery, hours, median (IQR)b | 26.6 (19.9-39.1) | 22.4 (17.6-32.1) | .067 |
| Time from surgery to discharge (days), median (IQR)b | 4 (3-6) | 3.5 (3-5) | .155 |

Abbreviation: IQR, interquartile range.
aValues of P are from Wilcoxon rank sum test for continuous variables and Fisher exact test for categorical numbers.
bSubset of patients with surgical treatment (pan-scan: Yes [N = 66], No [N = 232]).

workup did not expedite surgical intervention or early discharge. The FFS at our institution was established in 2012, and we feel that TTS and LOS being similar between cohorts is due to the maturity of this service. An institution with a less experienced FFS may have shown significantly increased TTS or LOS in patients who underwent CT pan-scans, which is concerning as unnecessary delays in surgical management in this patient population and has been linked to increased morbidity and mortality.22,23

Several studies have examined the benefits of CT pan-scans in the general trauma population. Whole-body CT imaging has been found to improve diagnostic accuracy, decrease time to diagnosis, decreased time to operative treatment, and reduction in overall mortality.13,14,16,17,24 However, this study did not support these findings when applied to the fragility fracture population. Other studies looking at elderly patients who sustain traumatic injuries have demonstrated no difference in injury severity and no impact on mortality when pan-scans were utilized in lower energy mechanisms.14,25,26 This discrepancy demonstrates that whole-body CT imaging has greater utility for younger patients and in higher energy trauma.

There is limited reporting in the literature on how CT pan-scans have altered specific patient care. Roberts et al and Kim et al both examined changes in care following whole-body CT imaging in low-risk patients. Roberts et al found that only 5% of their study population had an emergent intervention as a result of a CT pan-scan.25 Kim et al found only 3% of elderly trauma patients required some form of procedural intervention based on a CT pan-scan.12

Our study expands on these findings, as there was only 1 (0.92%) patient whose orthopedic management was changed based on the same imaging modality. Upon further investigation of this 1 patient, it is believed that such a change in management would have occurred even in the absence of a CT scan. This is due to the patient having a concern for an occult femur fracture, and a MRI is the gold standard study for ruling out this diagnosis.3,26-30 This patient required an MRI despite undergoing CT imaging. Our study also demonstrated that CT pan-scans did not improve TTS or decrease LOS in the fragility fracture patient population, which directly contradicts the patterns seen in younger patient populations.14,17

Our results support previous studies that have shown CT pan-scans in the elderly population have demonstrated a significant risk of incidental findings. The rate of unrelated findings in CT whole-body imaging has been reported as high as 50% and is known to be directly related to increasing age.14,15,26,31 In our patient cohort, 41.7% of those undergoing a whole-body CT scan had additional findings that did not impact their care. This raises the concern that CT pan-scans in low-risk patients, such as fracture fragility patients, significantly increases cost without much benefit.1,11,25 Our study also supports this as 88% of patients had no change in care after undergoing a CT pan-scan, and 13% of patients had consultations that resulted in no change in care. This rate of incidental findings has the potential to increase the complexity of care coordination for this patient population and could lead to much confusion. There is the additional concern, as the high contrast loads and radiation exposure related to CT pan-scans may be causing direct harm to these patients.1,13,14,21,25,31

This study is not without limitations. The retrospective single-center nature of the study design and the relatively small sample size represent the most significant limitations. Our institution lacks a robust protocol for conducting CT pan-scans, which introduced the potential for significant variability in which patients underwent this diagnostic workup. The retrospective nature also means that clinical documentation may not clearly reflect whether history or examination findings occurred before or after CT pan-scan findings. Patient demographic information did show there was no difference in age, BMI, or CCI between those who underwent CT pan-scan and those who did not. Also, while there is a relatively small sample size, other studies have demonstrated similar results with comparable patient numbers. Ultimately, a prospective study with a larger sample size could provide more definitive evidence.

In conclusion, the benefits of CT pan-scans are questionable for patients who sustain fragility fractures. This patient population inherently has a high incidence of findings demonstrated
on whole-body CT scan that do not ultimately impact management. This presents a risk of unnecessarily increasing healthcare costs and radiation exposure in this patient population, whose baseline care coordination remains challenging. While a randomized controlled trial is necessary to further the findings presented in this study, whole-body CT imaging in fragility fracture patients demonstrates little benefit while further complicating their care with an increased rate of incidental findings.

Conclusion
This study demonstrates whole-body CT imaging provides little benefit in geriatric patients who sustain fragility fractures and should be utilized judiciously and in a targeted fashion instead of as a routine part of TS or ED protocol in this patient population.

Authors’ Note
Eric Lepkowsky contribution to study design, data collection, and manuscript preparation; Trevor Simcox contribution to data collection and manuscript preparation; Hunter Rogoff contribution to data collection; Omid Barzideh contribution to study design and manuscript preparation; and Shahidul Islam contribution to statistical analysis.

Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID ID
Eric Lepkowsky, MD https://orcid.org/0000-0002-1548-658X

References
1. Gartin CG, Reves J, Heimer SD, Haan JM. Injury patterns and incidence of intra-abdominal injuries in elderly ground level fall patients: is the pan-scan warranted? Am J Surg. 2019;218(5):847-850.
2. Cauley J. Public health impact of osteoporosis. J Gerontol A Biol Sci Med Sci. 2013;68(10):1243-1251.
3. Reske-Nielsen C, Medzon R. Geriatric trauma. Emerg Med Clin N Am. 2016;34(3):483-500.
4. Bergström U, Björnstig U, Stenlund H, Jonsson H, Svensson O. Fracture mechanisms and fracture pattern in men and women aged 50 years and older: a study of a 12-year population-based injury register, Umeå, Sweden. Osteoporos Int. 2008;19(9):1275-1275.
5. Desforges J, Tinetti M, Speechley M. Prevention of falls among the elderly. N Engl J Med. 1989;320(16):1055-1059.
6. Hsu R, Ramirez JM, Blankenhorn BD. Surgical considerations for osteoporosis in ankle fracture fixation. Orthop Clin North Am. 2019;50(2):245-258.
7. Mitchell P, Åkesson K. How to prevent the next fracture. Injury. 2018;49(8):1424-1429.
8. World Health Organization. Guidelines for Preclinical Evaluation and Clinical Trials in Osteoporosis. Geneva, Switzerland: World Health Organization(WHO); 1998.
9. Crandall CJ, Larson J, Manson JE, et al. A comparison of U.S. and Canadian osteoporosis screening and treatment strategies in postmenopausal women. J Bone Miner Res. 2018;34(4):607-615.
10. Kim J, Herbert B, Hao J, Min W, Zirah BH, Mauffrey C. Acetabular fractures in elderly patients: a comparative study of low-energy versus high-energy injuries. Int Orthop. 2015;39(6):1175-1179.
11. Hruska K, Ruge T. The tragically hip. Emerg Med Clin N Am. 2018;36(1):219-235.
12. Kim C, Sartin R, Dissanaike S. Is a “pan-scan” indicated in the older patient with a ground level fall? Am Surg. 2018;84(9):1480-1483.
13. Çorbacıoğlu ŞK, Aksel G. Whole body computed tomography in multi trauma patients: review of the current literature. Turk J Emerg Med. 2018;18(4):142-147.
14. Sierink JC, Treskes K, Edwards MJ, et al. Immediate total-body CT scanning versus conventional imaging and selective CT scanning in patients with severe trauma (REACT-2): a randomised controlled trial. Lancet. 2016;388(10045):673-683.
15. Seah MK, Murphy CG, McDonald S, Carothers A. Incidental findings on whole-body trauma computed tomography: experience at a major trauma centre. Injury. 2016;47(3):691-694.
16. Dwyer CR, Scifres AM, Stahlfeld KR, et al. Radiographic assessment of ground-level falls in elderly patients: is the “pan-scan” overdoing it? Surgery. 2013;154(4):816-822.
17. Topp T, Lefering R, Lopez CL, Ruchholz S, Ertel W, Kühne CA. Radiologic diagnostic procedures in severely injured patients—is only whole-body multislice computed tomography the answer? Int J Emerg Med. 2015;8(1):3.
18. Tosounidis TI, Giannoudis PV. Pelvic fractures presenting with haemodynamic instability: treatment options and outcomes. Surgeon. 2013;11(6):344-351.
19. Yu L, Baumann BM, Raja AS, et al. Blunt traumatic aortic injury in the pan-scan era. Acad Emerg Med. 2019. doi:10.1111/acem.13900.
20. Gioffrè-Florio M, Murabito LM, Visali C, Pergolizzi FP, Fam’a F. Trauma in elderly patients: a study of prevalence, comorbidities and gender differences. G Chir. 2018;39(1):35-40.
21. Engström U, Björnstig U, Stenlund H, Jonsson H, Svensson O. Fracture mechanisms and fracture pattern in men and women aged 50 years and older: a study of a 12-year population-based injury register, Umeå, Sweden. Osteoporos Int. 2008;19(9):1275-1275.
22. Desforges J, Tinetti M, Speechley M. Prevention of falls among the elderly. N Engl J Med. 1989;320(16):1055-1059.
23. Hsu R, Ramirez JM, Blankenhorn BD. Surgical considerations for osteoporosis in ankle fracture fixation. Orthop Clin North Am. 2019;50(2):245-258.
24. Mitchell P, Akesson K. How to prevent the next fracture. Injury. 2018;49(8):1424-1429.
abdominal-pelvic injury. Rev Esp Anestesiol Reanim (English Edition). 2018;65(6):323-328.

25. Roberts J, Watts S, Klim S, Ritchie P, Kelly AM. Yield of serious axial injury from pan scans after blunt trauma in haemodynamically stable low-risk trauma patients. Emerg Med Australas. 2018;31(3):399-404.

26. James MK, Schubl SD, Francois MP, Doughlin GK, Lee SW. Introduction of a pan-scan protocol for blunt trauma activations: what are the consequences? Am J Emerg Med. 2017;35(1):13-19.

27. Kellock TT, Khurana B, Mandell JC. Diagnostic performance of CT for occult proximal femoral fractures: a systematic review and meta-analysis. AJR Am J Roentgenol. 2019;213(6):1324-1330.

28. Pejic A, Hansson S, Rogmark C. Magnetic resonance imaging for verifying hip fracture diagnosis why, when and how? Injury. 2017;48(3):687-691.

29. Raval P, Mayne AIW, Yeap PM, Oliver TB, Jariwala A, Sripada S. (2019). Outcomes of magnetic resonance imaging detected occult neck of femur fractures: do they represent a less severe injury with improved outcomes? Hip Pelvis. 2019;31(1):18-22.

30. Sadozai Z, Davies R, Warner J. The sensitivity of CT scans in diagnosing occult femoral neck fractures. Injury. 2016;47(12):2769-2771.

31. Fakler JK. Retrospective analysis of incidental non-trauma associated findings in severely injured patients identified by whole-body spiral CT scans. Patient Saf Surg. 2014;8(36). doi: 10.1186/s13037-014-0036-3.