Title
Risk Factors Associated With Infection in Open Fractures of the Upper and Lower Extremities.

Permalink
https://escholarship.org/uc/item/9c68919f

Journal
Journal of the American Academy of Orthopaedic Surgeons. Global research & reviews, 4(12)

ISSN
2474-7661

Authors
Tornetta, Paul
Della Rocca, Gregory J
Morshed, Saam
et al

Publication Date
2020-12-08

DOI
10.5435/jaaosglobal-d-20-00188

Peer reviewed
Risk Factors Associated With Infection in Open Fractures of the Upper and Lower Extremities

Paul Tornetta III, MD
Gregory J. Della Rocca, MD, PhD, FACS
Saam Morshed, MD
Clifford Jones, MD, FACS
Diane Heels-Ansdell, MSc
Sheila Sprague, PhD
Brad Petrisor, MD, MSc, FRCSC
Kyle J. Jeray, MD
Gina Del Fabbro, BPH
Sofia Bzovsky, MSc
Mohit Bhandari, MD, PhD, FRCSC
on behalf of the FLOW Investigators

Abstract

Introduction: Open fractures are associated with a high risk of infection. The prevention of infection is the single most important goal, influencing perioperative care of patients with open fractures. Using data from 2,500 participants with open fracture wounds enrolled in the Fluid Lavage of Open Wounds trial, we conducted a multivariable analysis to determine the factors that are associated with infections 12 months postfracture.

Methods: Eighteen predictor variables were identified for infection a priori from baseline data, fracture characteristics, and surgical data from the Fluid Lavage of Open Wounds trial. Twelve predictor variables were identified for deep infection, which included both surgically and nonoperatively managed infections. We used multivariable Cox proportional hazards regression analyses to identify the factors associated with infection. Irrigation solution and pressure were included as variables in the analysis. The results were reported as adjusted hazard ratios (HRs), 95% confidence intervals (CIs), and associated P values. All tests were two tailed with alpha = 0.05.

Results: Factors associated with any infection were fracture location (tibia: HR 5.13 versus upper extremity, 95% CI 3.28 to 8.02; other lower extremity: HR 3.63 versus upper extremity, 95% CI 2.38 to 5.55; overall P = 0.001), low energy injury (HR 1.64, 95% CI 1.08 to 2.46; P = 0.019), degree of wound contamination (severe: HR 2.12 versus mild, 95% CI 1.35 to 3.32; moderate: HR 1.08 versus mild, 95% CI 0.78 to 1.49; overall P = 0.004), and need for flap coverage (HR 1.82, 95% CI 1.11 to 2.99; P = 0.017).

Discussion: The results of this study provide a better understanding of which factors are associated with a greater risk of infection in open fractures. In addition, it can allow for surgeons to better counsel patients regarding prognosis, helping patients to understand their individual risk of infection.
Open fractures are associated with a high risk of infection.\textsuperscript{1-8} Infection of an open fracture in the upper or lower extremities is associated with poorer outcomes, including increased rates of delayed union and nonunion, increased length of hospital stay, and lower health-related quality of life.\textsuperscript{1-3,8} The results from the Fluid Lavage of Open Wounds (FLOW) trial have confirmed that patients who had an infection or another complication that required an additional surgery reported notably lower physical and mental health-related quality of life in the 12 months after their fracture compared with those who did not have an infection.\textsuperscript{9} The sequelae of infections continue to be a cause of prolonged morbidity, prolonged hospitalization, and even death.\textsuperscript{10}

Although previous investigations being conducted on the predictive risk factors for infection, none have evaluated a large multicenter data set.\textsuperscript{11-15} The purpose of this study was to determine the factors associated with infection in a large prospective series of open fractures of the upper and lower extremities treated at multiple centers.

## Methods

### Fluid Lavage of Open Wounds Trial

The FLOW trial was a multicenter, blinded, randomized controlled trial, using a $2 \times 3$ factorial design that evaluated irrigation solution (soap versus normal saline) and irrigation pressure (very low versus low versus high) in participants with open fracture wounds.\textsuperscript{9} Research ethics board approval for the FLOW trial was obtained at the coordinating center.
Participants were randomized using an internet-based randomization system, which ensured concealed randomization of eligible consenting patients. Participants were followed for 12 months from their injury for assessment of clinical outcomes. The primary outcome in FLOW was a composite of reoperation, defined as surgery that occurred within 12 months after the initial procedure to treat an infection at the surgical site or contiguous to it, manage a wound-healing problem, or promote bone healing. Secondary clinical outcomes included nonoperatively managed infections, wound, or fracture healing complications. All clinical outcomes were adjudicated by an independent Adjudication Committee.

The trial included 2,447 participants across 41 clinical sites in the United States, Canada, Australia, Norway, and India. The FLOW primary analysis found soap to have a notably higher reoperation rate than saline and found no differences between the three irrigation pressures evaluated.16

Selection of Predictor Variables
Based on biologic rationale and previous reports in the literature, we identified potential predictor variables a priori from the baseline, fracture characteristics, and surgical data collected as part of the FLOW trial. These were chosen by the FLOW Steering Committee based on previous literature and experience. We identified 18 predictor variables for infection within 12 months (Table 1), and 12 predictor variables for deep infection, including both surgically and nonoperatively managed infections (Table 2). It was methodologically necessary to include both irrigation pressure and solution as variables in all analyses because they were the basis of the initial FLOW trial. When selecting our predictor variables for the analysis, we ensured that at least 10 events were found for each parameter to avoid having an over fitted or unstable mode.17

Definition of Infection
Infection in participants was defined as a constellation of clinical symptoms and laboratory examinations and classified according to the Center for Disease Control criteria.10 These included, but were not limited to, fever, erythema/ cellulites, positive tissue cultures, and frank purulent drainage occurring within 12 months from the initial procedure. When interpreting the criteria, any infections that were superficial to the fascia were considered to be “superficial incisional surgical site infections,” and any infections that were deep to the fascia were considered to be “deep incisional surgical site infection” (including infections of the bone [osteomyelitis]). The central adjudication committee adjudicated all reported infections to determine whether they met the Center for Disease Control criteria and classified them as superficial or deep.

Data Analysis—Predictors of Infection and Deep Infection
We conducted two multivariable Cox proportional hazards regression analyses with time to any infection and time to deep infection as the dependent variables to identify the factors associated with the outcome. Participants with complete data for all selected predictor variables were included in the analyses. The results were reported as adjusted hazard ratios (HRs), 95% confidence intervals (CIs), and associated P values. All tests were two tailed with alpha = 0.05.

Results

Participant Characteristics
Seven participants with delayed definitive fixation who experienced an infection before definitive fixation were excluded from the analysis. This left a total of 2,338 participants with complete data for the selected predictor variables who were included in the Cox proportional hazards regression analysis with time to infection as the independent variable. Their mean age was 45.1 years. Most were men (69.4%) and had a lower extremity fracture (68.8%) (Table 1). Of the participants included in this analysis, 289 (12.4%) experienced either a superficial or deep infection within 12 months of initial surgery and 156 (6.7%) experienced a deep infection during that time.

Predictors of Any Infection
The factors associated with any infection were fracture location (tibia: HR 5.13 versus upper extremity, 95% CI 3.28 to 8.02; other lower extremity: HR 3.63 versus upper extremity, 95% CI 2.38 to 5.55; overall P < 0.001), low energy injury (HR 1.63, 95% CI 1.08 to 2.46; P = 0.019), degree of wound contamination (severe: HR 2.12 versus mild, 95% CI 1.35 to 3.32; moderate: HR 1.08 versus mild, 95% CI 0.78 to 1.49; overall P = 0.004), and need for flap coverage (HR 1.82, 95% CI 1.11 to 2.99; P = 0.017) (Table 1).

Predictors of Deep Infection
The factors associated with deep infection were location (tibia: HR 2.72 versus upper extremity, 95% CI 1.57 to 4.71; other lower extremity: HR 2.98 versus upper extremity, 95% CI 1.72 to 5.18; overall P < 0.001), Gustilo Type III fracture (HR 1.57, 95% CI 1.09 to 2.27; P = 0.016), delayed wound closure (wound not closed at initial irrigation and...
débridement) (HR 1.89, 95% CI 1.24 to 2.90; \( P = 0.003 \)), and need for flap coverage (HR 2.05, 95% CI 1.14 to 3.71; \( P = 0.017 \)) (Table 2).

### Discussion

Our analysis of FLOW data found that patients with lower extremity fractures, especially tibia fractures, compared with upper extremity fractures, were at a higher risk of infection. In addition, high energy

### Table 1

Factors Associated With Infection in Open Fractures (n = 2,338; 289 events)

| Independent Variable | Incidence of Predictors, n (%) | Adjusted HR (95% CI) | \( P \) Value |
|----------------------|-------------------------------|----------------------|-------------|
| Fracture location    |                               |                      | <0.001      |
| Tibia                | 883 (37.8)                    | 5.13 (3.28-8.02)     |             |
| Other lower extremity| 726 (31.1)                    | 3.63 (2.38-5.55)     |             |
| Upper extremity      | 729 (31.2)                    | 1.00                 |             |
| Low-energy mechanism of injury | 280 (12.0) | 1.63 (1.08-2.46) | 0.019 |
| Degree of contamination |                               |                      | 0.004       |
| Mild                 | 1,799 (76.9)                  | 1.00                 |             |
| Moderate             | 416 (17.8)                    | 1.08 (0.78-1.49)     |             |
| Severe               | 123 (5.3)                     | 2.12 (1.35-3.32)     |             |
| Age (10-yr increase) | 45.1 (17.8) mean (SD)         | 1.04 (0.96-1.12)     | 0.376       |
| Male sex             | 1,622 (69.4)                  | 1.05 (0.79-1.39)     | 0.733       |
| Current smoker       | 754 (32.2)                    | 1.08 (0.84-1.40)     | 0.537       |
| Other major injury\(^a\) | 722 (30.9) | 0.91 (0.69-1.19) | 0.496 |
| Comminuted or segmental fracture | 1,579 (67.5) | 1.21 (0.91-1.60) | 0.182 |
| Bone loss            | 512 (21.9)                    | 1.19 (0.90-1.58)     | 0.223       |
| Method of definitive fixation |                               |                      | 0.148       |
| Nail                 | 792 (33.9)                    | 1.00                 |             |
| Plate                | 1,177 (50.3)                  | 1.36 (0.997-1.86)    |             |
| Other                | 369 (15.8)                    | 1.30 (0.86-1.98)     |             |
| Bone grafting at initial surgery | 50 (2.1) | 0.95 (0.35-2.60) | 0.918 |
| Type III postoperative Gustilo type | 846 (36.2) | 1.23 (0.92-1.64) | 0.161 |
| Total operating time \( \geq 120 \) min | 997 (42.6) | 1.11 (0.86-1.44) | 0.429 |
| Time to first incision from injury |                               |                      | 0.126       |
| \(<6 \) hr           | 465 (19.9)                    | 1.00                 |             |
| \(6-12 \) hr         | 980 (41.9)                    | 0.92 (0.68-1.23)     |             |
| \(>12-24 \) hr       | 785 (33.6)                    | 0.71 (0.50-1.02)     |             |
| \(>24 \) hr          | 108 (4.6)                     | 1.27 (0.66-2.43)     |             |
| Delayed wound closure (wound not closed at initial irrigation and débridement) | 373 (16.0) | 0.95 (0.66-1.38) | 0.796 |
| Randomized solution  |                               |                      | 0.922       |
| Soap                 | 1,178 (50.4)                  | 1.1 (0.80-1.28)      |             |
| Saline               | 1,160 (49.6)                  | 1.00                 |             |
| Randomized pressure  |                               |                      | 0.833       |
| High                 | 784 (33.5)                    | 1.00                 |             |
| Low                  | 772 (33.0)                    | 1.05 (0.79-1.41)     |             |
| Very low             | 782 (33.4)                    | 1.09 (0.82-1.46)     |             |
| Time-dependent variables | Wound flap | 108 (4.6) | 1.82 (1.11-2.99) | 0.017 |

CI = confidence interval, HR = hazard ratio

\(^a\) At least one of the following: femoral fracture, pelvic fracture, spinal fracture, liver injury, bowel injury, splenic injury, other abdominal injury, hemo/pneumothorax, closed head injury, urogenital injury, traumatic amputation, vascular injury, lung contusion, thoracic injury, hip fracture, and spinal injury.
injuries, wounds with severe and moderate contaminations, and wounds that required flap coverage were associated with infection. Factors associated with deep infections included lower extremity factors, especially tibia fractures, compared with upper extremity fractures, Gustilo Type III injuries, fractures requiring delayed wound closure (wound not closed at initial irrigation and débridement), and the need for flap coverage. Interestingly, we did not find any patient factors (age, sex, and smokers) or treatment factors (method of fixation and timing of surgery) to be predictive of infection. All predictive factors were related to the severity of the injury.

Participants with a lower extremity open fracture compared with those with an upper extremity open fracture were found to be at an increased risk of any infection and of a deep infection. These findings coincide with a recent meta-analysis that examined fracture location in two randomized controlled trials, seven prospective, and 18 retrospective studies. The study found that lower extremity fractures were at a notably higher risk of developing infectious complications (11.8% versus 5.4%; risk ratio (RR) 1.94, \( P < 0.0001 \)). Moreover, a retrospective study found that the tibia had an increased odds ratio for infection of 2.44 (95% CI 1.26 to 4.73) when compared with non-tibial injury.

As expected, we found that worse injuries have higher complication rates. As demonstrated in other investigations, we were unable to find an association between infection and patient factors (age, sex, and smokers) nor treatment factors (method of fixation and timing of surgery).

In a prospective study of 480 participants, the investigators did not find smoking status to be a

### Table 2

**Factors Associated With Deep Infection in Open Fractures (n = 2,346; 156 events)**

| Independent Variable | Incidence of Predictors, n (%) | Adjusted HR (95% CI) | \( P \) Value |
|----------------------|-------------------------------|----------------------|---------------|
| Fracture location    |                               |                      |               |
| Tibia                | 885 (37.7)                    | 2.72 (1.57-4.71)     | <0.001        |
| Other lower extremity| 729 (31.1)                    | 2.98 (1.72-5.18)     |               |
| Upper extremity      | 732 (31.2)                    | 1.00                 |               |
| Delayed wound closure (wound not closed at initial irrigation and débridement) | 380 (16.2) | 1.89 (1.24-2.90) | 0.003 |
| Type III postoperative Gustilo type | 852 (36.3) | 1.57 (1.09-2.27) | 0.016 |
| Age (10-yr increase) | 45.1 (17.7) mean (SD)         | 1.07 (0.96-1.18)     | 0.220         |
| Male sex             | 1,626 (69.3)                  | 0.92 (0.64-1.33)     | 0.663         |
| Current smoker       | 758 (32.3)                    | 1.03 (0.73-1.47)     | 0.855         |
| Other major injury\( ^a \) | 724 (30.9) | 1.03 (0.72-1.45) | 0.892 |
| Total operating time ≥120 min | 1,000 (42.6) | 0.98 (0.69-1.39) | 0.921 |
| Time to first incision from injury | | | |
| <6 hr | 467 (19.9) | 1.00 |
| 6-12 hr | 985 (42.0) | 0.77 (0.52-1.13) | 0.083 |
| >12-24 hr | 786 (33.5) | 0.54 (0.34-0.87) |
| >24 hr | 108 (4.6) | 0.88 (0.36-2.16) |
| Randomized solution  |                               |                      |               |
| Soap                | 1,181 (50.3)                  | 0.99 (0.72-1.36)     | 0.955         |
| Saline              | 1,165 (49.7)                  | 1.00                 |               |
| Randomized pressure |                               |                      |               |
| High                | 787 (33.5)                    | 1.00                 |               |
| Low                 | 774 (33.0)                    | 1.10 (0.75-1.62)     | 0.817         |
| Very low            | 785 (33.5)                    | 0.98 (0.66-1.46)     |               |
| Time-dependent variables |                 |                      |               |
| Wound flap          | 110 (4.7) ever                | 2.05 (1.14-3.71)     | 0.017         |

\( CI = \) confidence interval, \( HR = \) hazard ratio

\( ^a \) At least one of the following: femoral fracture, pelvic fracture, spinal fracture, liver injury, bowel injury, splenic injury, other abdominal injury, hemothorax, closed head injury, urogenital injury, traumatic amputation, vascular injury, lung contusion, thoracic injury, hip fracture, and spinal injury.
statistically notable factor for infection. Furthermore, a retrospective study of 1,043 participants with an open fracture of the ankle did not find a statistically notable association between smoking and postoperative infection. Similarly, a retrospective review of 478 patients with open ankle fractures showed no correlation between patient-reported smoking and wound complications, including infection, after ankle fracture surgery.

Fractures managed with flaps were at a higher risk of infection that is similar to other studies. Furthermore, delayed wound closure was found to be associated with deep infection. These findings are likely driven by the severity of the injury because simpler wounds are closed initially.

To our knowledge, few studies have prospectively enrolled large numbers of open fractures, particularly including upper extremity injuries. The primary strength of this study is the preplanned analysis of 2,338 open fractures from 41 clinical sites in the United States, Canada, Australia, Norway, and India, giving this secondary analysis a more robust basis for predicting infection and secondary intervention. The large sample size and diversity of participants allows for greater generalizability of our findings and increases the external validity of our results. Furthermore, the use of the Cox proportional hazards regression allowed for the control of potentially confounding variables.

However, this study has several limitations. First, because of missing data, it was not feasible to include all 2,447 participants from the FLOW trial in this analysis. In addition, this analysis was limited by the variables collected as part of the FLOW trial. As a result, some factors potentially associated with infection may not have been collected and were not included in this analysis.

In conclusion, recognizing risk factors associated with infections in open fractures is important in preventing these infections and other complications that impede the healing process. This data set gives us more information to risk adjust and understand the factors leading to infection in open fractures. These findings can allow surgeons to better advise patients about treatment and prognosis and set appropriate expectations. Future research should focus on exploring methods to reduce infection in this high risk cohort. Finally, the results of this study may inform future research by identifying a need for large, prospective research, particularly on the lower extremities.

Appendix 1

FLOW Investigators

Steering Committee: Mohit Bhandari (Chair, McMaster University), Gordon H. Guyatt (Co-Chair, McMaster University), Kyle J. Jeray (Co-Chair, Greenville Health System), Stephen D. Walter (McMaster University), Brad Petrisor (McMaster University), Emil H. Schemitsch (St. Michael’s Hospital), Paul Tornetta III (Boston University Medical Center), Jeff Anglen (Eskenazi Health Services, Indiana University), Michael Bosse (Carolinas Health Care System), Susan Liew (The Alfred), Parag Sancheti (Sancheti Institute for Orthopaedics and Rehabilitation)

Global Methods Center: Mohit Bhandari (Principal Investigator); Sheila Sprague (Research Methodologist); Paula McKay, Kim Madden, Terry Coady, Mark Macleod, Debra Bartley, Christina Tieszer. Queen Elizabeth II Health Sciences Centre—David Sanders, Abdel-Rahman Lawyendy, Kevin Gurr, Timothy Carey, Chris Bailey, Mark Macleod, debra Bartley, Christina Tieszer.

Data Monitoring Committee: Douglas Altman (University of Oxford), Rajiv Gandhi (Toronto Western Hospital), Markus Bischoff (McMaster University)

Adjudication Committee: Mohit Bhandari (McMaster University), Gregory J. Della Rocca (University of Missouri Health Care), Brad Petrisor (McMaster University), Kyle J. Jeray (Greenville Health System), Emil H. Schemitsch (St. Michael’s Hospital)

Participating Clinical Sites:
Canada—Hamilton Health Sciences—Brad Petrisor, Bill Ristevski, Krishan Rajaratnam, Dale Williams, Matthew Denkers, Drew Bednar, John Sadler, Desmond Kwok, Mohit Bhandari, Brian Drew, Ivan Wong, Paula McKay, Kim Madden, Kerry Tai. St. Michael’s Hospital—Jeremy A. Hall, Michael D. McKee, Emil H. Schemitsch, Henry Ahn, Daniel Whelan, James Waddell, Timothy Daniels, Earl Bogoch, Aaron Nauth, Milena R. Vicente, Jennifer T. Hidy. London Health Sciences Centre—David Sanders, Abdel-Rahman Lawyendy, Kevin Gurr, Timothy Carey, Chris Bailey, Mark Macleod, Debra Bartley, Christina Tieszer.

Queen Elizabeth II Health Sciences Centre—Chad Coles, Ross Leighton, C. Glen Richardson, Michael Bidulph, Michael Gross, Michael Dunbar, J. David Amiraault, David Alexander, Catherine Coady, Mark Glazebrook, David Johnston, William Oxner, J. Andrew Trenholm, Gerald Reardon, Kelly Trask, Shelley MacDonald. The Ottawa Hospital Civic Campus—Steven Papp, Wade Gofron, Allan Liew, Stephen Kingwell, Joseph O’Neill, Garth Johnson, Eugene Wai, Julia Foxall. Vancouver General Hospital—Henry M. Broekhuysen, Peter J. O’Brien, Piotr A. Blachut, Kelly A. Lefaire, Raman Johal. Hôpital du Sacré-Coeur de Montréal—Stéphane Leduc, G. Yves Laflamme, Pierre Beaumont, Michel Malo, Benoit Benoit, Dominique...
References

1. Wordsworth M, Lawton G, Nathwani D, et al: Improving the care of patients with severe open fractures of the tibia. Bone Joint J 2016;98-B:420-424.

2. Penn-Barwell JG, Bennett PM, Mortiboy DE, Fries CA, Groom AFG, Sargeant ID: Factors influencing infection in 10 years of battlefield open tibia fractures. Strag Trauma Limb Reconstr 2016;11:13-18.

3. Blair JA, Stoops TK, Doarn MC, et al: Infection and nonunion after fasciotomy for compartment syndrome associated with tibia fractures: A matched cohort comparison. J Ortop Trauma 2016;30:392-396.

4. Metsemakers WJ, Handojo K, Vanderschot P, Nijs S: Individual risk factors for deep infection and compromised fracture healing after intramedullary nailing of tibial shaft fractures: A single centre experience of 480 patients. Injury 2015;46:740-745.

5. Lack WD, Karunakar MA, Angerame MR, et al: Type III open tibia fractures: Immediate antibiotic prophylaxis minimizes infection. J Ortop Trauma 2015;29:1-6.

6. Krstakis I, Giannoudi M, Giannoudis PV: Infection rates after open tibial fractures: Are they decreasing? Injury 2014;45:1023-1027.

7. Matos MA, Carvo-Filho RN, da Silva BVP: Risk factors associated with infection in tibial open fractures. Rev Fac Ciencias Medicas 2013;70:14-18.

8. Ortamal R, Beig A, Schnechen EMM, Verhoef MJD: Risk factors for infectious complications after open fractures: a systematic review and meta-analysis. Int Ortoph 2017;41:1965-1982.

9. Kortmann R, Beig St, St, et al: Flare flap coverage in the management of open fracture wounds. Clin J Med 2015;373:1290-1294.

10. Centers for Disease Control and Prevention. Surgical Site Infection (SSI) Event; 2017. https://www.cdc.gov/hsnss/pdf/psscurrent.pdf. Accessed January 30, 2019.

11. Dubina AG, Paryavi E, Mountain TT, Allmon C, O'Toole RV: Surgical site infection in tibial plateau fractures with ipsilateral compartment syndrome. Injury 2017;48:495-500.

12. Hull PD, Johnson SC, Stephen DJ, Kreder HJ, Jenkinson RJ: Delayed debridement of severe open fractures is associated with a higher rate of deep infection. Bone Joint J 2014;96 B:379-384.

13. Jenkinson RJ, Kiss A, Johnson S, Stephen DJ, Kreder HJ: Delayed wound closure increases deep-infection rate associated with lower-grade open fractures. J Bone Joint Surg Am 2014;96:380-386.

14. Elniep AR, Gannoudis PV: Open fractures of the lower extremity. EORTC Open Rev J 2018;3:316-325.

15. Saleeb H, Tousoudis T, Papakostidis C, Giannoudis PV. Incidence of deep infection, union and malunion for open diaphyseal tibial fractures treated with IM nailing: A systematic review. Surgeon 2019; 17:257-269.

16. Investigators FLOW: Fluid Lavage of Open Wounds (FLOW): Design and rationale for a large, multicentre collaborative 2x3 factorial trial of irrigating pressures and solutions in patients with open fractures. BMC Musculoskelet Disord 2010;6:85.

17. Peduzzi P, Conato J, Kemper E, Hoford TR, Feinstein AR: A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996; 49:1373-1379.

18. Weber D, Dulai SK, Bergman J, Buckley R, Beaupre LA: Time to initial operative treatment following open fracture does not impact development of deep infection: A prospective cohort study of 736 subjects. J Ortop Trauma 2012;28:613-619.

19. Scolaro JA, Schenker ML, Yannascoli S, Baldwin K, Mehta S, Ahn J: Cigarette smoking increases complications following fracture: A systematic review. J Bone Joint Surg Am 2014;96:674-681.

20. Enninghorst N, McDougal D, Hunt JJ, Balogh ZJ: Open tibia fractures: Timely debridement leaves injury severity as the only determinant of poor outcome. J Trauma 2011;70:352-357.

21. Olsen LL, Møller AM, Brorson S, Hasselager RB, Sort R: The impact of lifestyle risk factors on the rate of infection after surgery for a fracture of the ankle. Bone Joint J 2017;99-B:225-230.

22. Miller AG, Margules A, Raikin SM: Risk factors for wound complications after ankle fracture surgery. J Bone Joint Surg Am 2012;94:2047-2052.

23. De’alleyrand JC, Mannon TT, Dancy L, et al: Is time to flap coverage of open tibial fractures an independent predictor of flap-related complications? J Ortop Trauma 2014;28:288-293.

24. Chua W, De SD, Lin WK, Bagda F, Murphy D. Early versus late flap coverage for open tibial fractures. J Orthop Trauma 2015;29:2047-2052.

25. Cheng H, Hsu Y, Wu C: Risk of infection with delayed wound coverage by using negative-pressure wound therapy in Gustilo grade IIIB/IIIC open tibial fracture: An evidence based review. J Plast Reconstr Aesthet Surg 2013;66:876-878.