Risk Factors for Infectious Complications after Open Fractures; A Systematic Review and Meta-analysis

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Abstract

Purpose To identify risk factors for the development of infection after open fracture fixation.

Methods A comprehensive search in all scientific literature of the last 30 years was performed in order to identify patient-, trauma-, diagnosis- and treatment-related risk factors. Studies were included when infectious complications were assessed in light of one or more risk factors. A meta-analysis was performed. Risk Ratios (RR) or Risk Differences (RD) with 95% confidence intervals were calculated.

Results 116 Manuscripts were included. Male gender (RR 1.42), DM (RR 1.72), smoking (RR1.29), a lower extremity fracture (RR 1.94), Gustilo-Anderson grade III open fracture (RR 3.01), contaminated fracture (RR 7.85) and polytrauma patients (RR 1.49) were identified as statistically significant risk factors for the development of infectious complications. Of the treatment related risk factors, only pulsatile lavage was associated with a higher infectious complication rate (RR 2.70).

Conclusion A number of risk factors for the development of infections after open fractures have been identified in the available literature. These factors should still be tested for independence in a multivariable model. Prospective, observational studies are needed to identify and quantify individual risk factors for infection after open fracture fixation.

Keywords: Open fractures; fracture fixation; infectious complications; risk factors

Introduction

The development of infectious complications after open fractures is an often encountered problem, with a rate ranging from <1% in grade I open fractures to 30% in grade III fractures[1-3]. Infections can be classified as acute, which includes superficial and deep soft tissue infections, and chronic infections, which are almost always bone infections, *i.e.*, osteomyelitis[4]. Although the guidelines are quite clear, the use of these definitions in clinical practice is poor, and terms are often used interchangeably. It is important to keep in mind that even seemingly innocent superficial wound infections can progress into chronic osteomyelitis, of which the consequences can be severe. Patients often require more than one surgical debridement, are prescribed many different antibiotics, and still, the rate of amputation due to chronic osteomyelitis or severe soft tissue infection ranges from 4.2 to 10.6%[5-7]. Preventing infection should therefore be one of the main goals in the primary treatment of a patient with a severe soft tissue injury[8].

Many patient- and treatment-related factors are believed to influence the development of infectious complications, but to date, a risk assessment model has not yet been established. Such a model could be a valuable aid for clinicians, helping them in delivering patient-tailored care. Risk assessment models have been proven helpful in clinical practice, of which the APACHE-II score for the risk of mortality of newly admitted ICU patients is one of the most well-known[9]. But efforts have also been made to create risk models for the development of complications after trauma[10, 11].

There are a number of guidelines discussing protocols for debridement, fracture stabilization, and antibiotic prophylaxis[12, 13]. Some variations exist between hospitals, and local protocols may deviate from the described guidelines. In addition, the guidelines are based on a general population, and although some specifications are made (*e.g.*, for Gustilo-Anderson grade), many other patient- or trauma-related risk factors are not taken into account. A large

number of studies have assessed one or more risk factors in relation to infectious complications after open fractures, but many studies are retrospective, and populations are often small.

The aim of this study was to perform a systematic review and provide an overview of the risk factors for infectious complications in open fractures.

Methods

All aspects of the Cochrane Handbook for Interventional Systematic Reviews were followed and the study was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[14]. In addition, the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines were used to assess case series[15]. Supplementary Figure 1 provides an overview of the definitions used in this review[4, 16].

Literature search strategy

A comprehensive search was performed with the help of a biomedical information specialist on March 30 2015 and updated on August 1st 2016, in Embase, Cochrane, Google Scholar, Medline (OvidSP), PubMed publisher and Web-of-Science. Only articles written in English were included, but no other limits were applied. Search strings for each database are provided in Appendix 1. All references were screened by the first reviewer (KK), and in case of doubt a second reviewer (MHJV) was consulted. In case of disagreement, a third reviewer would have been consulted, but consensus was reached for every case. Study selection was accomplished through two phases. During the first phase, titles and abstracts were reviewed for relevance, and full-text articles were obtained. Published meeting abstracts of which a full text was not yet published were excluded in order to prevent bias. During the second phase, full-text articles were reviewed.

Studies were included when infectious complications were assessed in light of one or more potential risk factors. Each demographic, trauma-, injury- or treatment related factor that was described in the literature was included, there was no predefined list of factors to specifically search for. Only studies published within the last 30 years were included. Studies reporting on less than 50 patients were excluded. Studies only assessing treatment of non- or malunion, or long-term osteomyelitis occurring after 90 days as the only outcome measure were excluded, as were all animal studies.

An additional comparison was made between open and closed fractures, in order to assess whether an open fracture itself was a risk factor for infections. For this purpose, all articles found in the initial search that also included closed fractures were identified.

Full-text articles presenting preliminary results were included if they contained detailed data regarding infectious complications and one or more risk factors, and a full-text article describing the final data was not available. If data were unclear or pooled for closed and open fractures, the authors were requested to provide data for the open fracture subgroup alone. Authors were also contacted when two or more publications seemed to overlap. If no response was obtained after two reminders, articles with pooled or unclear fracture description were excluded. In cases of evident overlap, either the largest or most recent cohort was included. All references of included full text articles were manually screened in order to ensure that no relevant articles were missed.

Data extraction and critical appraisal

Data were collected on study design, population, affected bones, risk factors, and infectious complications. This was primarily done by one reviewer (KK), and in case of doubt a second reviewer (MHJV) was consulted. The level of evidence of each paper was established using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) tool. The GRADE approach defines the quality of a body of evidence by consideration of risk of bias

(methodological quality), directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias.

Meta-analysis

A meta-analysis was performed using SPSS version 21 and Review Manager version 5.3 (The Nordic Cochrane Center, Copenhagen, Denmark). Forest plots were created for the different risk factors encountered in the included studies. The first group of analyses was based on patient- and trauma-related factors. The last part consisted of analyses of treatment course-related factors.

Patients with a certain potential risk factor were compared to those without that specific factor. Heterogeneity between studies was assessed by two methods. First, a Chi^2 test was conducted, with a P-value <0.1 being considered statistically significant. In addition, I^2 statistics were performed, using a cut-off point of 40%. If no heterogeneity was observed a fixed effect model was used. If heterogeneity (I^2>40%) remained present regardless of selectivity analysis, a random effect model was used. Results are presented in Risk Ratios (RR) or Risk Differences (RD) with a p-value or 95% CI. P-values <0.05 were considered statistically significant. Forest plots were created to schematically demonstrate the effect of each risk factor. If heterogeneity was present, sensitivity analyses were performed for study design (*i.e.*, only RCTs or only prospective studies), population (*i.e.*, more than 100 or 250 patients) and year of publication (*i.e.*, published after 2000).

Results

A total of 3,490 unique studies were identified in the search. The flowchart in Figure 1 shows the selection process. Eleven authors were contacted, but unfortunately, either split data were not available or no response was obtained.

<<< Figure 1 >>>

After final selection 116 articles remained for inclusion in this review describing a total of 20,367 fractures (a reliable number of patients could not be calculated). The majority of included studies (n=79) were retrospective case series. Only eight randomized controlled trials (RCTs) were included, and the remaining 30 were prospective studies. A total of 17 pre-treatment potential risk factors, and eight treatment related potential risk factors were identified. The quality of evidence of the included studies was assessed per risk factor. Evidence on Gustilo-Anderson grade and antibiotic prophylaxis could be rated “moderate” if only RCTs were included, but evidence on all other risk factors was rated “low” or “very low” according to the GRADE criteria. The overview tables of quality of evidence per risk factor are attached as supplementary material (Appendix II). An overview of each risk factor found, and its association with the development of infectious complications in open fractures, is presented in Table 1.

<<< Table 1>>>

Part I – patient and trauma-related factors

Age

Thirteen articles mentioned age as a risk factor, most reported mean age (N=10, 1,819 fractures),[8, 17-25] others median age (N=3, 1,477 fractures)[26-28]. Using those that presented age in means with standard deviations (SD) did not demonstrate significant differences between infected and non-infected patients.

Body Mass Index (BMI)

BMI was only described in two articles[8, 19], both reporting mean values with SD. No significant difference was encountered between those with and without infectious complications.

Gender

Thirteen studies compared male and female patients (one RCT, three prospective and nine retrospective studies)[8, 17-21, 23-25, 29-32]. Male patients have a higher risk for developing infections: 16.1 versus 11.6%, RR 1.42, p=0.004 (Figure 2).

<<< Figure 2 >>>

Ethnicity

One study compared Caucasian patients to non-Caucasian patients, and found no significant difference in infection rate, although 25.2 versus 10.5% may imply clinical relevance [23].

American Society of Anesthesiologists (ASA)-score

Two studies included the ASA-score in their risk analysis, however, one used a mean number of points with standard deviation[25] and the other a cut-off point of 2[24]. Neither found significant differences between the two groups.

Diabetes Mellitus

Five studies described the rate of infectious complications in relation to diabetes (DM)[23-25, 27, 33]. Patients with DM developed significantly more post-traumatic infections: 25.3% versus 13.8%, RR =1.72, p=0.01 (figure 3).

<<< FIGURE 3 >>>

Human Immuno-deficiency Virus (HIV)

Only two studies assessed HIV status[34, 35] Both were prospective cohort studies, HIV status was tested prospectively on admission in one study and retrospectively assessed in the other, allowing for possible bias. Although infection rate in HIV negative patients was lower than in HIV positive patients (21.0% versus 13.1%), no significant difference was observed (p=0.35).

Hypertension and systemic vascular disease

Two studies described either hypertension[23] or systemic vascular disease[24]. The first found no significant difference, but Molina *et al.* detected a higher incidence of infections in patients with systemic vascular disease (37.8 versus 18.1%, p=0.01). When bundled, a trend to significance was observed: 21.6 versus 18.6%, RR 1.60, p=0.07.

Smoking, Alcohol, and Drugs

Eleven studies (three prospective, eight retrospective) compared smokers with non-smokers with regard to infectious complications after open fractures[20, 23-25, 27, 33, 36-40]. Smokers had a significantly increased risk of infections: 17.7 versus 13.8%, RR 1.29, p=0.04

<<< FIGURE 4 >>>

Alcohol was discussed in three articles[24, 25, 39] and drug use in two[25, 39]. . No significant differences in rate of infections were observed in these relatively small populations.

Fracture localization

A total of 27 studies described different fracture localizations (two RCTs, seven prospective and 18 retrospective studies, 6,425 fractures)[21, 22, 25, 28, 29, 32, 41-61]. Four only defined "upper" and "lower" extremity[21, 25, 42, 61], but the rest actually mentioned two or more specific bones. First, upper extremity fractures were compared to lower extremity fractures[21, 22, 28, 29, 32, 41-53]. The latter were significantly more prone to developing infectious complications; 11.8% versus 5.4% (RR 1.94, p=<0.0001, Figure 5). However, there was significant heterogeneity between studies (p=0.02, I^2=44%). Sensitivity analysis was performed, but excluding either retrospective or older studies (*i.e.*, publication date before 2000) did not result in less heterogeneity, nor did setting stricter limits for populations (*i.e.*, more than 100 or more than 250 included patients).

<<< Figure 5 >>>

Second, infectious complications in specific bones were assessed. Calcaneal fractures demonstrated the highest univariate infection rate (25%). However, calcaneal fractures were only specified in two articles[32, 44], adding up to four patients in total. Probably due to this small sample size, no significant difference was demonstrated (p=0.09), even though the risk ratio for calcaneal fractures was 3.30 (95% CI 0.84-12.89).

The second highest infectious complication rate was seen in ankle fractures (20.7%, Table 1), which were described in nine studies[22, 32, 43, 48, 50, 51, 53, 60, 62]. There was no significant heterogeneity between these studies. Ankle fractures demonstrated a trend to statistical significance, with regard to infectious complications: RR 1.42, p=0.07. Femur (p=0.73)

and tibia (p=0.11) fractures[22, 28, 29, 32, 41, 43-46, 48-51, 53-60, 62] did not demonstrate an increased risk of infections when individually compared to all other fractures, nor did any of the upper extremity fractures.

Open versus closed fractures

To assess whether open fractures alone were a risk factor for infections, they were compared to closed fractures. This resulted in a total of 51 articles[53, 56, 63-111], representing 2,980 open and 7,893 closed fractures. Infection rates were 4.2% for closed and 10.6% for open fractures. However, significant heterogeneity was detected when including all 51 articles. Excluding all retrospective case series eliminated this. Infections were still more frequently observed after open fractures; 11.4 versus 7.0% (RR 2.60, p<0.001, Figure 6).

<<< Figure 6 >>>

Gustilo-Anderson classification

Most studies compared the three groups within the Gustilo-Anderson classification (N=84, 16,331 fractures)[8, 17-19, 21, 24-26, 29, 30, 33, 35, 36, 39, 41-44, 46-51, 54, 56, 59, 67, 72, 76, 79, 94, 100, 111-161]. Infection rates in grade III fractures was significantly higher than in grade I & II fractures (15.9% versus 5.1%; RR 3.01, p<0.00001). Due to the multitude of studies heterogeneity was present (I^2 = 47%). Excluding all retrospective studies still resulted in significant heterogeneity. When only randomized controlled trials were included (N=5, 691 fractures)[50, 131, 132, 142, 160], heterogeneity was eliminated (I^2= 0%), and statistically significant differences were still present: 19.2 versus 7.2%, RR 2.63, p<0.0001 (Figure 7).

<<< Figure 7 >>>

Contamination

Three studies (one prospective, two retrospective, 880 fractures)[17, 29, 39] described contamination as a risk factor for infectious complications after open fractures. Although there was significant heterogeneity between studies, infections did occur more often in patients with contaminated wounds (RR 7.85, p=0.002, figure 8).

<<<figure 8>>>

Trauma mechanism

Only three articles compared different trauma mechanisms, two prospective and one retrospective study (612 fractures)[22, 39, 53]. First, motor vehicle accidents (MVA) were compared to all other mechanisms of injury. No significant differences in infectious complication rates were observed. Pedestrians, gunshot wounds (GSW) and farmyard injuries were individually compared to all other mechanisms of injury due to their vulnerability or specific characteristics. The first two did not demonstrate any difference in risk ratios, however, farmyard injuries (although only described in one study) demonstrated significantly increased risk of infections: 100% versus 10.5% (Table 2, RR 7.22, p=0.0001).

Polytrauma versus monotrauma

Four studies identified patients with polytrauma or monotrauma (one RCT, one prospective, two retrospective, 741 patients)[25, 32, 123, 129]. Infections developed more often in polytrauma patients (RR 1.49, p=0.03, Figure 9).

<<< Figure 9 >>>

Injury Severity Score (ISS)

ISS was the most difficult factor to analyze. Although it was described in a total of ten articles, it was presented in a different manner in most of them. Four studies used cut-off points, <13, <18 and <25[17, 29, 37, 123]. Four other studies used mean values for infected and non-infected fractures[18, 20, 22, 52], and the remaining two others used median values[27, 28]. Regardless of different presentations, no statistically significant association between ISS score and infection rates could be detected.

Part II – treatment related risk factors

Antibiotic prophylaxis and timing thereof

One prospective and two retrospective studies discussed the rate of infectious complications in relation to the timing of antibiotic prophylaxis[33, 46, 162]. No significant difference was encountered (RR 1.29, p=0.52) between early and late administration. In addition, there was some variability between the used cut-off points; two studies used a three hour limit to define early versus delayed, the third split their group in three; <2 hours, 2-4 hours and >4 hours.

Two RCTs compared antibiotic prophylaxis with placebo[32, 163]. There was significant heterogeneity between the two studies (I^2=49%), which can be explained by the fact that Braun[32] excluded finger fractures where Stevenson only included phalangeal fractures[163].

Timing of debridement

Eighteen studies (one RCT, three prospective, 17 retrospective)[19, 33, 44, 46-48, 112, 113, 117, 124, 135, 150, 160, 162, 164-170] regarded infectious complications in relation to timing of debridement. As with antibiotic prophylaxis, cut-off points varied (limits set on five, six, eight or twelve hours), and selection bias may very well be present. No significant difference was observed between the early and the delayed group (RR 1.00, p=0.99).

Pulsatile Lavage

One article included pulsatile lavage as a potential risk factor for the development of infections, and found that it was indeed related to a higher infection rate as compared to high volume, low pressure washout of the fracture: 24 versus 9%, p=0.04[24].

Fixation method

Internal fixation was compared to external fixation in 16 studies (four RCTs, five prospective, eight retrospective)[8, 21, 22, 24, 35, 39, 50, 54, 114, 115, 118, 141, 171-175]. Heterogeneity was large (p=<0.00001, I^2=79%); sensitivity analysis did not change this. Either way, no differences were encountered between the two techniques: 20.7% infections for internal fixation versus 23.6% for external fixation (p=0.55). Including only RCTs to minimalize possible selection bias did not change this. Still, no apparent difference was observed between the internal or external fixation of open fractures (p=0.16).

Delayed wound closure

Immediate versus delayed wound closure was addressed in four studies, two prospective and two retrospective[39, 123, 138, 151]. No differences were seen in the development of infectious complications (RR 0.95, p=0.91), but again selection bias may have been present. A fifth study compared wound closure <72 hours with closure >72 hours after trauma, and found no difference in infection rate. However; when patients who underwent single-stage orthoplastic fixation and coverage were compared to those who had multiple reconstructive surgeries, a difference was found in favor of the single-stage patients: 4.2% versus 34.6% developed an infectious complication (p<0.001)[176].

Blood transfusion

Only two studies described blood transfusion as a risk factor for infectious complications[22, 41]. Both were prospective, and no heterogeneity was encountered. With 13.7% infections for patients who did receive a blood transfusion versus 6.2% for those who did not, blood transfusion seems to be a risk factor for the development of infectious complications (RR 2.08, p=0.0004, Figure 10).

<<< Figure 10 >>>

Splenectomy

Only one study compared patients who underwent splenectomy with patients who did not[177]. Infectious complication rates were evidently increased for the first group; 25.0 versus 4.7%. With a RR of 5.38 splenectomy seems to be a risk factor for the development of infections, but due to the small number of patients this did not reach statistical significance (p=0.07).

Discussion

This systematic review and meta-analysis are, to the best of our knowledge, the first to bundle all available evidence regarding risk factors for infectious complications after surgically treated open fractures. An extensive literature search has been performed, and a large number of articles were found, comprising more than 20,000 individual fractures. A number of factors were identified that seem to increase the infectious complication rate: male gender, DM, smoking, polytrauma status, lower extremity fractures, Gustilo-Anderson grade III fractures and contaminated wounds.

Unfortunately, the level of evidence was low, and caution is warranted with the interpretation of these results. Possible confounding cannot be detected by means of a meta-analysis, and multivariable analysis of a large study population should be performed in order to assess this issue. Some other possible risk factors, which have been demonstrated to influence the development of infectious complications in elective general surgical and orthopedic procedures (*e.g.* BMI[178], alcohol/drug abuse[179-181]) were not identified as risk factors in this meta-analysis. This may again be explained by the low levels of evidence of the included studies, the possibility of confounding, and the fact that some factors were only sporadically described in the available literature, and population numbers were too low to detect statistical significance. A large number of other possible risk factors were not addressed at all in the identified studies, but may still be important in the development of infections after open fracture treatment (*e.g.*, malnutrition, renal disease,[182, 183], liver disease[184, 185]).

This meta-analysis has a number of limitations. Many studies were retrospective, making data less reliable. Smaller studies (*i.e.*, less than 50 patients) were excluded to prevent false negative results. Because of the prevalence of many risk factors in the general population, chances are that these risk factors would not be present at all within a small study group.

Moreover, including these small studies would not increase the grade of evidence of this meta-analysis.

For some risk factors selection bias was highly suspected. It is, for instance, conceivable that external fixation may have been the treatment of choice in Gustilo-Anderson grade III fractures where internal fixation would have been chosen for the majority of grade I fractures. Gosselin *et al.* showed that antibiotic prophylaxis prevents infection in patients with open fractures[186]. The focus in this review was on timing of antibiotic prophylaxis, but it is again quite understandable that patients with Gustilo-Anderson grade III fractures were more likely to undergo debridement and receive antibiotic prophylaxis sooner than those with grade I fractures. Unfortunately, most articles only described either the Gustilo-Anderson grade in relation to infections, or the treatment modality. It is thus hard to deduct which factor presents the largest risk of infectious complications.

Heterogeneity between studies was a problem for a number of analyses. A number of studies only included Gustilo-Anderson grade III fractures, which in itself is a risk factor for infectious complications. Whether these studies can be compared with studies pooling all grades is debatable. Some studies were conducted in a pediatric population, which could account for a lower complication rate. The extremities included in the different studies varied, which may also result in heterogeneity. As has been previously demonstrated, lower extremity fractures are at greater risk for the development of infectious complications[41, 43, 49, 53], and it may not be valid to compare studies only including tibial fractures with those that pool upper and lower extremity fractures and publish one infectious complication rate for the entire study population. Some authors separately reported superficial and deep infections, others only included those patients who developed deep infections and yet others did not further specify their outcome. Overall, the definition for infection, as well as for the included risk factors varied between the studies.

Ideally, reliably quantified risk factors should be assembled into a mathematical formula that can predict the infection risk for an individual patient and guide therapeutic strategies. However, the current data are insufficient to build such a risk-assessment model. Although some risk factors were identified, these should still be tested for independence in a multivariable model. On the other hand, factors that have been investigated but did not appear to be risk factors for infection in this meta-analysis might have been erroneously excluded, due to, for instance, small sample sizes or confounding. The only way to improve the reliability and quantitative influence of the possible risk factors for infection, is a large, prospective database, incorporating all imaginable risk factors. Only after such a study, a high-quality risk-assessment model can be built. Once the data for such a model is available, the methods previously described by de Jongh *et al.[10]* could serve as a guideline to develop the infection prediction model.

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Compliance with Ethical Standards

Conflict of Interest

The authors have no conflicts of interest to disclose.

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Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent

Informed consent was not applicable in this study.

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Table 1. Possible risk factors for the development of postoperative infectious complications in open fractures.

Percentages between parentheses unless otherwise specified

Factor	No of articles	No of patients	Not infected	Infected	Heterogeneity		Outcome
Patient-Related Risk Factors					**Chi² (p-value)**	**I² (%)**	**RR, 95%CI**
Age (mean, SD)	10	1,819	40.3 (17.0)	41.4 (16.4)	6.69 (0.46)	0	1.48 -0.63-3.58[a]
BMI (mean, SD)	2	306	27.3 (5.5)	26.4 (6.6)	0.02 (0.88)	0	0.76, -0.85-2.36[a]
Male	13	1,485	1,246 (84)	239 (16)	11.25 (0.51)	0	1.42, 1.12-1.80
Female		681	602 (88)	79 (12)			
Caucasian	1	123	92 (75)	31 (25)	NA	NA	2.39, 0.62-9.20
Non Caucasian		19	17 (89)	2 (11)			
ASA-score >2	1	80	64 (80)	16 (20)	NA	NA	3.00, 0.73-12.27
ASA-score <2		30	28 (93)	2 (7)			
DM	5	79	59 (75)	20 (25)	1.27 (0.87)	0	1.72, 1.14-2.61
No DM		845	728 (86)	117 (14)			
HIV +	2	61	53 (87)	8 (13)	0.28 (0.60)	0	0.71, 0.35-1.45
HIV -		143	113 (79)	30 (21)			
Vascular disease	2	134	105 (78)	29 (22)	3.24 (0.07)	69	1.60, 0.97-2.63
No vascular disease		118	96 (81)	22 (17)			
Smoking	11	594	489 (82)	105 (18)	4.26 (0.89)	0	1.29, 1.02-1.64
No smoking		1,131	975 (86)	156 (14)			
Alcohol[b]	3	225	182 (81)	43 (19)	1.45 (0.48)	0	1.39, 0.93-2.07
No alcohol[b]		290	250 (86)	40 (14)			
Drugs[b]	2	97	78 (80)	19 (20)	0.42 (0.52)	0	1.33, 0.82-2.17
No drugs[b]		308	262 (85)	46 (15)			
Fracture Related Risk Factors							
Upper extremity[c]	20	1,799	1,701 (95)	98 (5)	34.09 (0.02)	44[d]	0.51, 0.38-0.70

Clavicle	2	2	2 (100)	0	0.12 (0.72)	0	6.18, 1.02-37.45
Humerus	11	166	157 (95)	9 (5)	6.76 (0.75)	0	0.98, 0.57-1.69
Elbow	3	53	51 (96)	2 (4)	4.92 (0.09)	59[d]	0.87, 0.12-6.44
Forearm	11	554	529 (95)	25 (5)	13.09 (0.22)	24	0.69, 0.42-1.13
Hand	4	71	69 (97)	2 (3)	18.16 (<0.001)	83[d]	3.56, 0.48-26.59
Lower extremity[c]	20	4,146	3,657 (88)	489 (12)	34.09 (0.02)	44[d]	1.94, 1.42-2.66
Femur	21	744	644 (87)	100 (13)	9.07 (0.34)	12	0.91, 0.55-1.52
Tibia	21	4,614	4,060 (88)	554 (12)	47.29 (<0.001)	58[d]	1.29, 0.97-1.71
Knee	2	41	36 (88)	5 (12)	0.06 (0.81)	0	0.55, 0.23-1.29
Patella	4	25	24 (96)	1 (4)	2.07 (0.56)	0	1.69, 0.50-5.73
Ankle	9	179	142 (79)	37 (21)	6.22 (0.51)	0	1.42, 0.97-2.08
Calcaneus	2	4	3 (75)	1 (25)	0.01 (0.93)	0	3.3, 0.84-12.89
Foot	6	158	156 (99)	2 (1)	3.58 (0.61)	0	1.16, 0.86-1.55
Grade I		4,058	3,942 (97)	116 (3)			
Grade II	84	4,888	4,548 (93)	340 (7)	159.35 (<0.00001)	47	3.01, 2.55-3.55[e]
Grade III		6,338	5,332 (84)	1,006 (16)			
Contamination	3	428	348 (81)	80 (19)	5.09 (0.08)	61[d]	7.85, 2.09-29.40
No contamination		452	441 (97.6)	11 (2.4)			
Trauma Related Risk Factors							
Motorcycle	3[22, 39, 53]	157	127 (81)	30 (19)	0.76 (0.68)	0	1.40, 0.92-2.15
Automobile		144	132 (91.7)	12 (8.3)	0.45 (0.50)	0	0.53, 0.27-1.01
Pedestrian	2	185	155 (84)	30(16)	13.86 (0.001)	86[d]	1.17, 0.30-4.66
Assault without weapon	3 1	10	10 (100)	0	NA	NA	0.38, 0.02-5.74
Gunshot wound		51	49 (96.1)	2 (3.9)	5.28 (0.02)	81[d]	0.44, 0.01-16.63
Fall from height	2	19	13 (68)	6 (32)	NA	NA	3.16, 1.48-6.75
Farmyard injury	1 1	2	0	2 (100)	NA	NA	7.22, 2.64-19.74

Polytrauma	4	421	342 (81)	79 (19)	4.93 (0.18)	39	1.49, 1.05-2.13
Monotrauma		320	282 (88)	38 (12)			
Higher ISS	4	423	376 (89)	47 (11)	3.78 (0.29)	21	0.86, 0.61-1.20
Lower ISS		706	616 (87)	90 (13)			
Treatment Related Risk Factors							
AB	2	141	136 (96.5)	5 (3.5)	1.95 (0.16)	49[d]	0.35, 0.08-1.47
No AB		139	123 (88)	16 (12)			
AB >3hrs	3	335	302 (90.1)	33 (9.9)	0.44 (0.80)	0	1.29, 0.59-2.79
AB < 3hrs		92	85 (92.4)	7 (7.6)			
Debridement >6hrs	21	2,111	1,867 (88)	244 (12)	26.95 (0.14)	26	1.00, 0.85-1.18
Debridement <6hrs		2,202	1,964 (89)	238 (11)			
Internal fixation	17	987	783 (79)	204 (21)	77.63 (<0.00001)	79[d]	0.85, 0.50-1.44
External fixation		550	420 (76)	130 (24)			
Delayed wound closure		151	122 (81)	29 (19)	4.87 (0.18)	38	0.90, 0.52-1.56
Immediate wound closure	4	79	62 (78)	17 (22)			
Pulsatile lavage	1	54	41 (76)	13 (24)	NA	NA	2.70, 1.03-7.05
No pulsatile lavage		56	51 (91)	5 (8.9)			
Blood transfusion		322	278 (86)	44 (14)	0.00 (0.99)	0	2.08, 1.39-3.12
No blood transfusion	2	650	610 (93.8)	40 (6.2)			
Splenectomy	1	8	6 (75)	2 (25)	NA	NA	5.38, 0.88-32.81
No splenectomy		43	41 (95.3)	2 (4.7)			

RR, Risk Ratio; CI, Confidence Interval; SD, Standard Deviation; BMI, Body Mass Index; ASA – American Society of Anesthesiologists; DM, Diabetes Mellitus; HIV, Human Immuno-deficiency Virus; NA, Not Applicable; ISS, Injury Severity Score; AB, Antibiotics

a. Provided value is mean difference instead of Risk Ratio

b. As indicated by patients themselves, not measured at time of admission

c. Some articles did not specify individual bones, just upper versus lower extremity

d. Random effect model used

e. Grade III fractures are compared to grade I/II fractures combined

Figure legends

Figure 1 – Identified and final included articles during search and selection process

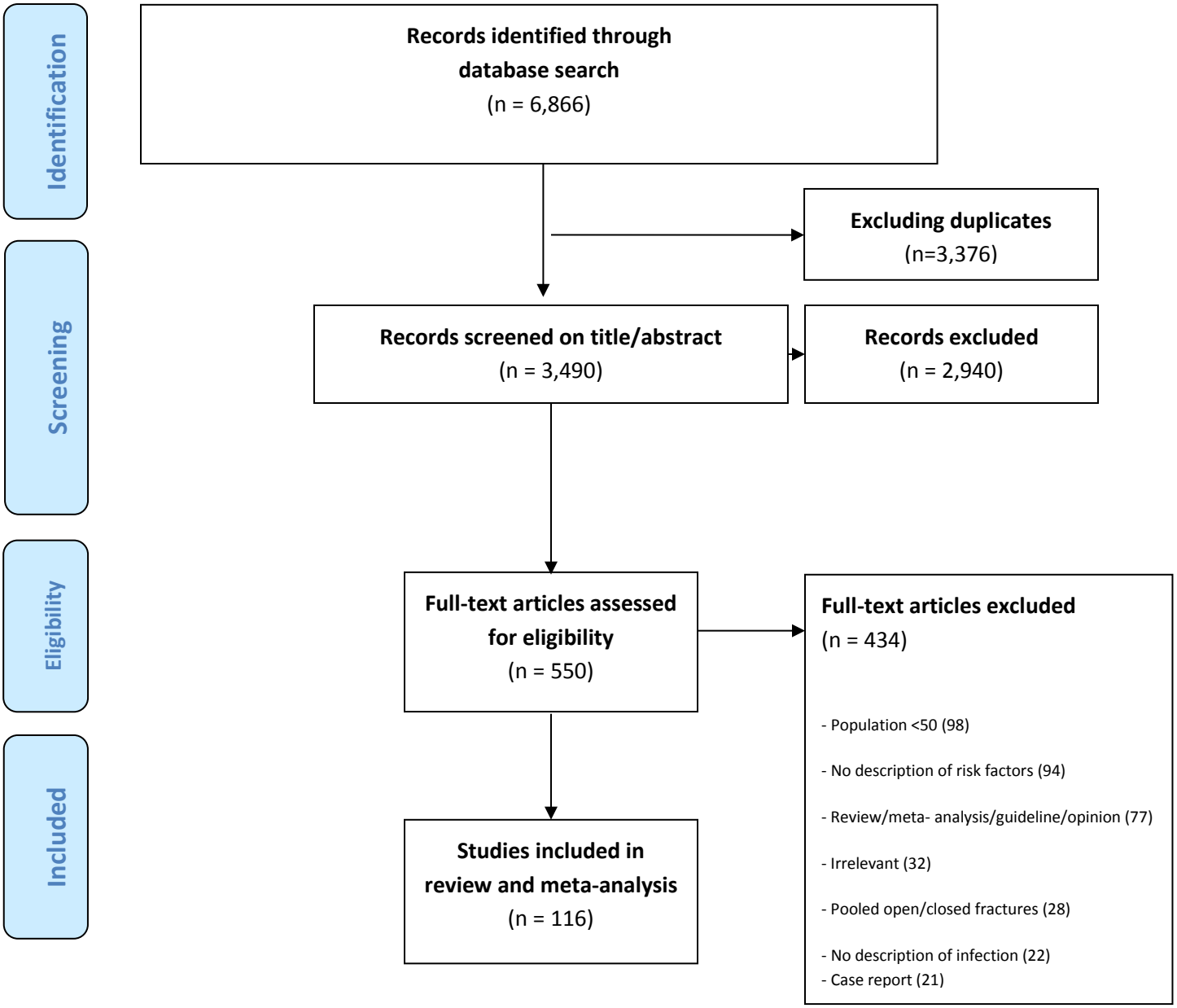

Figure 2 - Forest plot for infectious complications in male versus female patients with open fractures

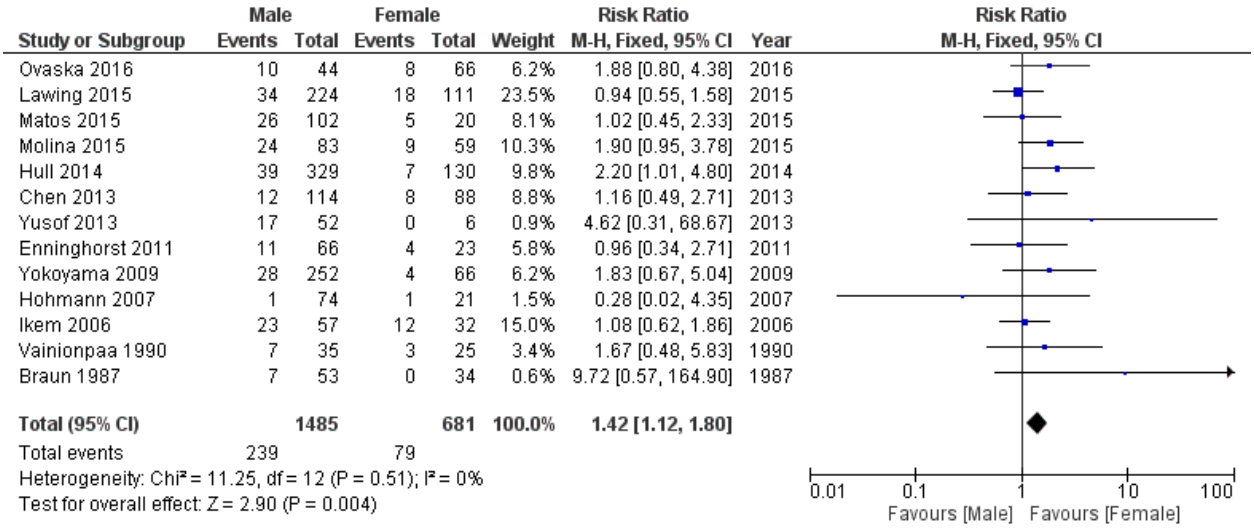

Figure 3 – Forest plot for infectious complications in patients with and without diabetes mellitus

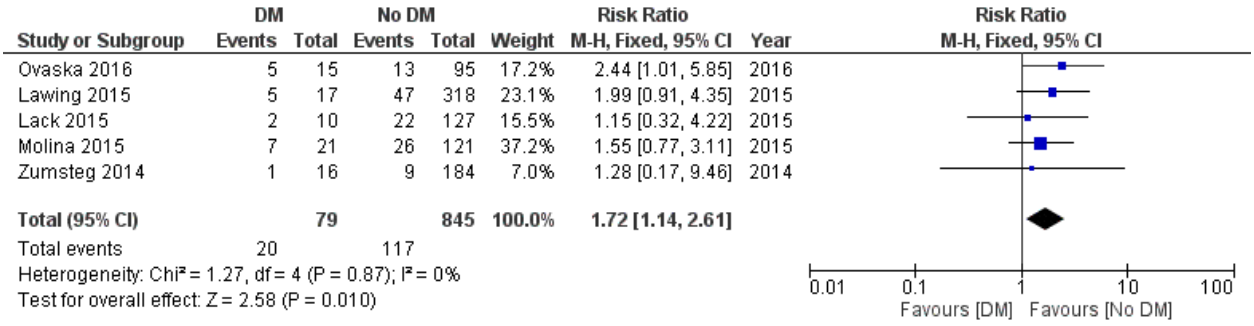

Figure 4 - Forest plot for infectious complications in smoking versus non-smoking patients

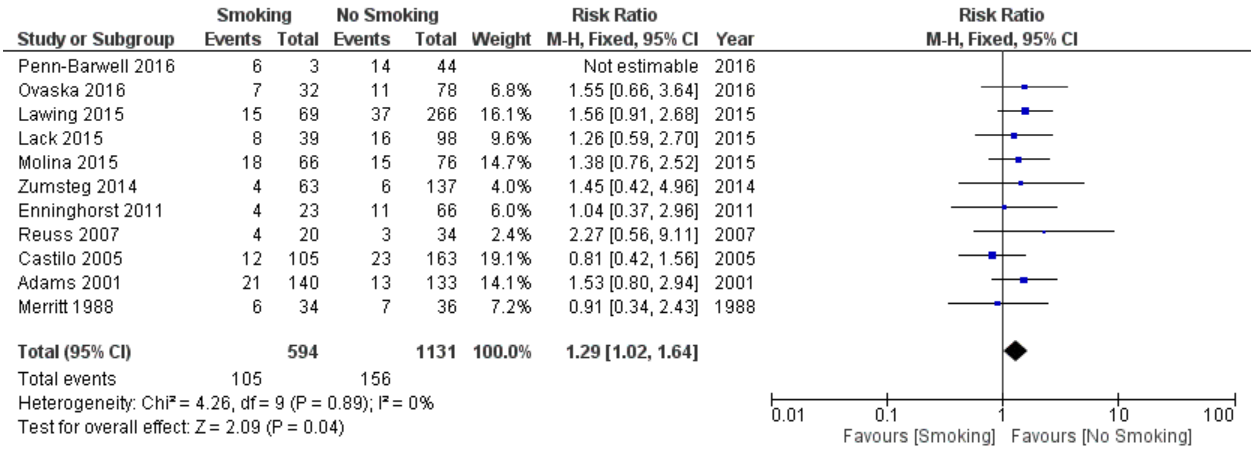

Figure 5 - Forest plot for infectious complications in patients with lower versus upper extremity fractures

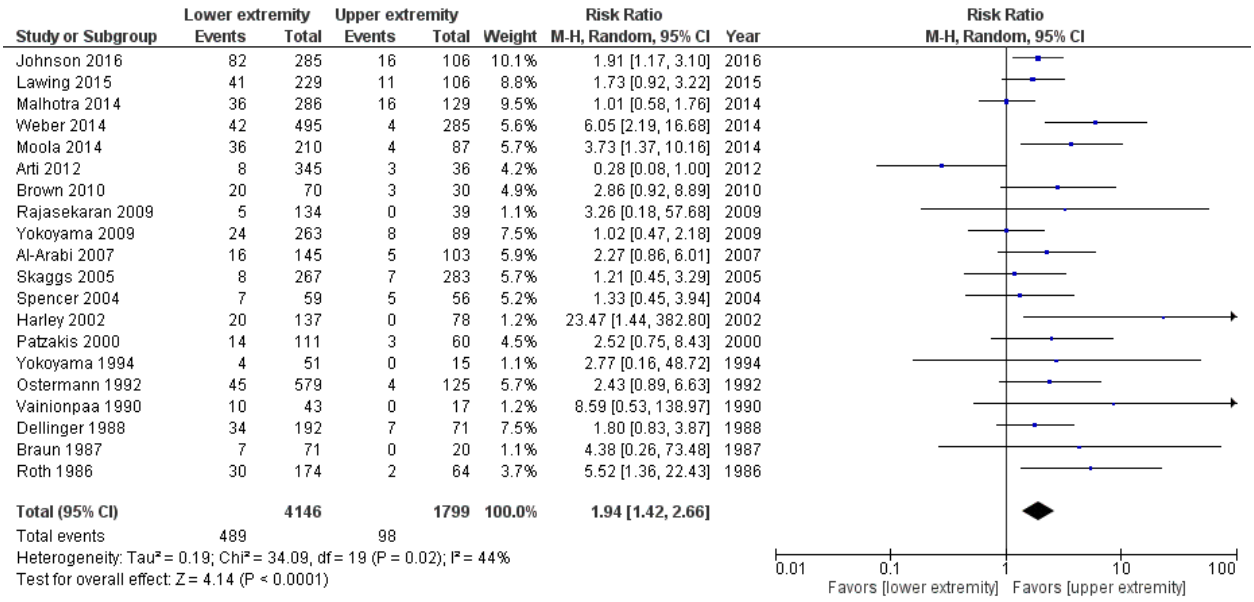

Figure 6 - Forest plot for infectious complications in patients with open versus closed fractures

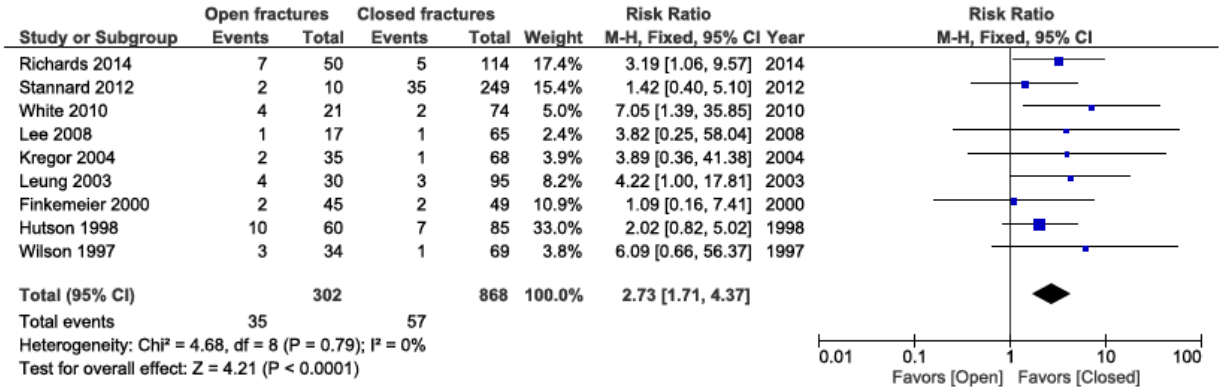

Figure 7 - Forest plot for infectious complications in patients with grade III versus grade I or II open fractures

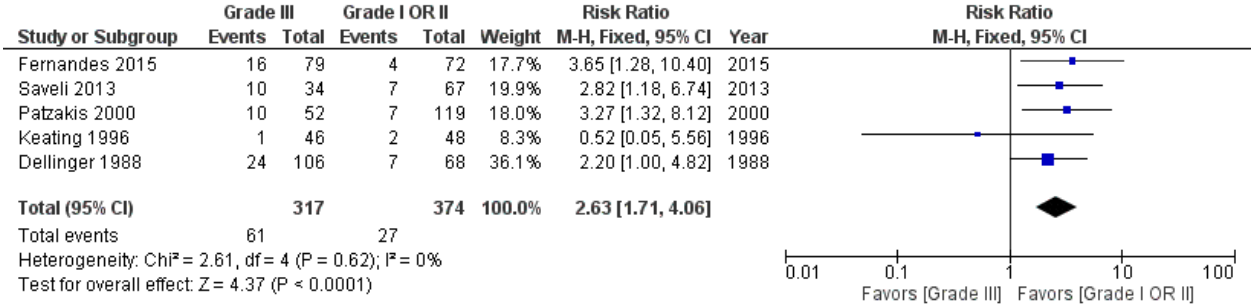

Figure 8 - Forest plot for infectious complications in patients with and without contamination of the wound

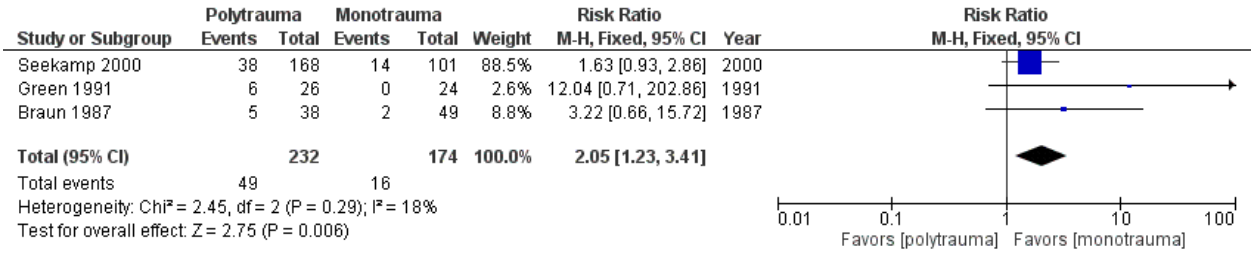

Figure 9 - Forest plot for infectious complications in polytrauma versus monotrauma patients with open fractures

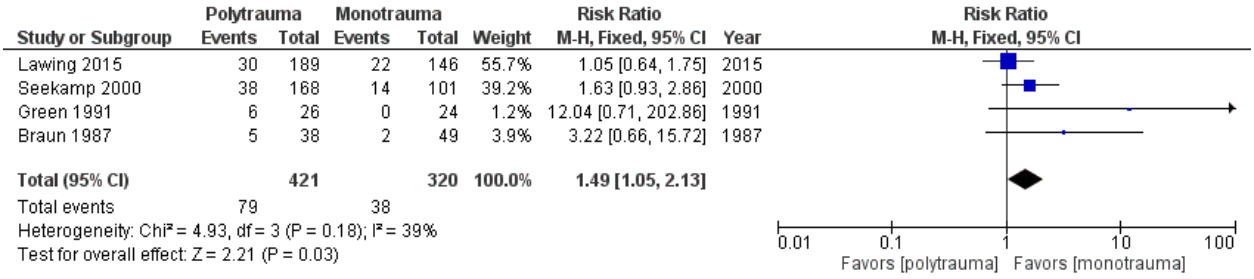

Figure 10 - Forest plot for infectious complications in patients with and without a blood transfusion