

Optimal timing of femur fracture stabilization in polytrauma patients: A practice management guideline from the Eastern Association for the Surgery of Trauma

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- BACKGROUND:** Femur fractures are common among trauma patients and are typically seen in patients with multiple injuries resulting from high-energy mechanisms. Internal fixation with intramedullary nailing is the ideal method of treatment; however, there is no consensus regarding the optimal timing for internal fixation. We critically evaluated the literature regarding the benefit of early (<24 hours) versus late (>24 hours) open reduction and internal fixation of open or closed femur fractures on mortality, infection, and venous thromboembolism (VTE) in trauma patients.
- METHODS:** A subcommittee of the Practice Management Guideline Committee of the Eastern Association for the Surgery of Trauma conducted a systematic review and meta-analysis for the earlier question. RevMan software was used to generate forest plots. Grading of Recommendations, Assessment, Development, and Evaluations methodology was used to rate the quality of the evidence, using GRADEpro software to create evidence tables.
- RESULTS:** No significant reduction in mortality was associated with early stabilization, with a risk ratio (RR) of 0.74 (95% confidence interval [CI], 0.50–1.08). The quality of evidence was rated as “low.” No significant reduction in infection (RR, 0.4; 95% CI, 0.10–1.6) or VTE (RR, 0.63; 95% CI, 0.37–1.07) was associated with early stabilization. The quality of evidence was rated “low.”
- CONCLUSION:** In trauma patients with open or closed femur fractures, we suggest early (<24 hours) open reduction and internal fracture fixation. This recommendation is conditional because the strength of the evidence is low. Early stabilization of femur fractures shows a trend (statistically insignificant) toward lower risk of infection, mortality, and VTE. Therefore, the panel concludes the desirable effects of early femur fracture stabilization probably outweigh the undesirable effects in most patients. (*J Trauma Acute Care Surg.* 2014;77: 787–795. Copyright © 2014 by Lippincott Williams & Wilkins)
- KEY WORDS:** Long bone stabilization; fracture fixation; timing fixation; early fixation; delayed fixation.
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Femur fractures are common among trauma patients and are typically seen in patients with multiple injuries resulting from high-energy mechanisms.¹ Internal fixation with intramedullary nailing is the ideal method of treatment. However, the optimal timing for internal fixation remains controversial.^{2–4} Proponents of early stabilization point to more desirable outcomes, such as fewer complications, shorter hospital stays, and lower costs of care.^{5–12} Opponents suggest that early definitive stabilization may not be safe for the most severely injured patients or those

with associated head, chest, or serious abdominal injuries due to increased blood loss, surgical stress, and pulmonary complications and that these and other factors may lead to increased mortality.^{13–17} Several other researchers have suggested a lack of benefit to early stabilization.^{18–25}

In 2001, an Eastern Association for the Surgery of Trauma (EAST) practice management guideline (PMG) promoted early stabilization of long bone fractures, including the femur, in polytrauma patients.⁶ EAST recently adopted the methodology of the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) for PMGs.^{26,27} The purpose of the current review was to update EAST’s femur fracture stabilization guidelines using GRADE methodology and systematic review. We critically evaluated the literature regarding the benefit of early (<24 hours) versus late (>24 hours) open reduction and internal fixation of open or closed femur fractures in trauma patients.

The GRADE methodology addresses many of the perceived shortcomings of existing models of evidence evaluation. Crucially, when using GRADE, the evidence is rated not by each study individually but across studies for specific clinical outcomes and evaluation of alternative management strategies. Evaluating clinical outcomes makes the guideline a useful and relevant tool for clinicians and, more importantly, for patients.²⁸

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OBJECTIVES

The objective of this guideline was to evaluate the comparative effectiveness of early (<24 hours) versus late (>24 hours) open reduction and internal fixation of an open or closed femur fracture in trauma patients, particularly in preventing mortality, infection, nonunion/malunion, amputation, and venous thromboembolism (VTE). Our PICO [Population, Intervention, Comparator, and Outcome] question is defined as follows:

Population: trauma patients with an open or closed femur fracture

Intervention: open reduction and internal fixation within 24 hours of injury

Comparator: open reduction and internal fixation greater than 24 hours after injury

Outcomes: mortality, infection, nonunion/malunion, amputation, VTE

INCLUSION CRITERIA FOR THIS REVIEW

Study Types

For the purpose of making recommendations, studies included randomized controlled trials (RCTs), prospective observational or retrospective studies, and case-control studies. Only studies pertaining to open reduction and internal fixation of open or closed femur fractures were included.

Participant Types

We included studies with adult patients, any sex, and with no restriction on inclusion of ethnicities or patients with comorbidities. Meta-analyses, case reports, letters, and reviews containing no original data or comments were excluded.

Intervention Type

We included studies comparing open reduction and internal fixation performed within 24 hours from the time of injury to stabilization performed greater than 24 hours after injury.

Outcome Measure Types

An initial list of all relevant outcomes (infection, nonunion/malunion, compartment syndrome, VTE, fat embolism syndrome, regional pain, neurologic impairment, arthritis, hardware failure, impaired function, mortality, or amputation) was generated and distributed to panelists. Eight panelists independently rated the relative importance of each outcome on a 9-point scale ranging from 1 (less important) to 9 (critically important for decision making). The five highest rated outcomes were selected as follows: mortality, infection, VTE, nonunion/malunion, and amputation. A systematic review of the literature was then conducted to identify relevant articles. Each article was evaluated independently by three members of the committee to extract pertinent data. We did not find any articles with data regarding the outcomes of nonunion/malunion and amputation, so these outcomes were excluded from the analysis.

Other outcomes considered were respiratory complications of fixation such as adult respiratory distress syndrome, fat embolism, pneumonia, and other pulmonary dysfunction. However, these outcomes were not included in this review.

REVIEW METHODS

Search Strategy

We conducted our literature search and appraisal based on guidelines for systematic reviews. A MEDLINE and Cochrane search was conducted to identify English language human subjects prospective RCTs, non-RCTs, existing systematic reviews, guidelines, case-control, and observational studies published before November 2013. Search terms included (1) *femoral fractures*, (2) *long bone stabilization*, (3) *timing fixation*, (4) *delayed fixation*, (5) *early fixation*, (6) *immediate fixation*, (7) *fracture fixation*, (8) *timing fracture*, and (9) timing osteosynthesis, alone or in combination. In addition to the electronic search, the bibliographies of relevant articles and systematic reviews were hand searched to find additional potentially appropriate publications to be included in this review.

Study Selection

A single panelist conducted the literature search and assessed the titles and abstracts to identify relevant publications, applying inclusion criteria. We excluded case reports and review articles. The resulting studies then underwent full-text review by three independent reviewers to determine appropriateness for inclusion.

Data Extraction and Management

Data were extracted by a single reviewer, confirmed by two other reviewers, and entered into Review Manager X.6 (RevMan). Information included authorship, publication year, methodology of the study, population, intervention, and relevant outcome measures.

Methodological Quality Assessment

The articles were evaluated using the GRADE system.²⁷⁻⁴⁰ The quality of evidence was classified as high, moderate, low, or insufficient for each outcome. The quality of evidence is reflected as the extent to which one can be confident that an estimate of effect is correct and includes an explicit consideration of the following domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias.³¹⁻³⁶ Recommendations were developed based on the results of the meta-analysis as well as the quality of evidence, and per the GRADE approach, they were classified as either "strong" or "weak".⁴¹ A strong recommendation, prefaced by the statement "we strongly recommend," indicates that the panel is certain the desirable consequences of a course of action outweigh the undesirable effects in most patients. A weak recommendation, prefaced by the statement "we conditionally recommend," indicates that the panel concludes the desirable effects of adherence to a recommendation probably outweighed the undesirable effects but it was not as confident. These recommendations were based on the quality of evidence and the risk-versus-benefit ratio.

Measures of Treatment Effect

We created a detailed set of evidence tables containing all abstracted information. Clinical outcomes, including mortality, infection, and VTE reported in each included study, were individually pooled for meta-analysis. The relative risk (RR) and 95% confidence interval (CI) were calculated for each study using a random-effects model.⁴² A $p < 0.05$ was considered significant

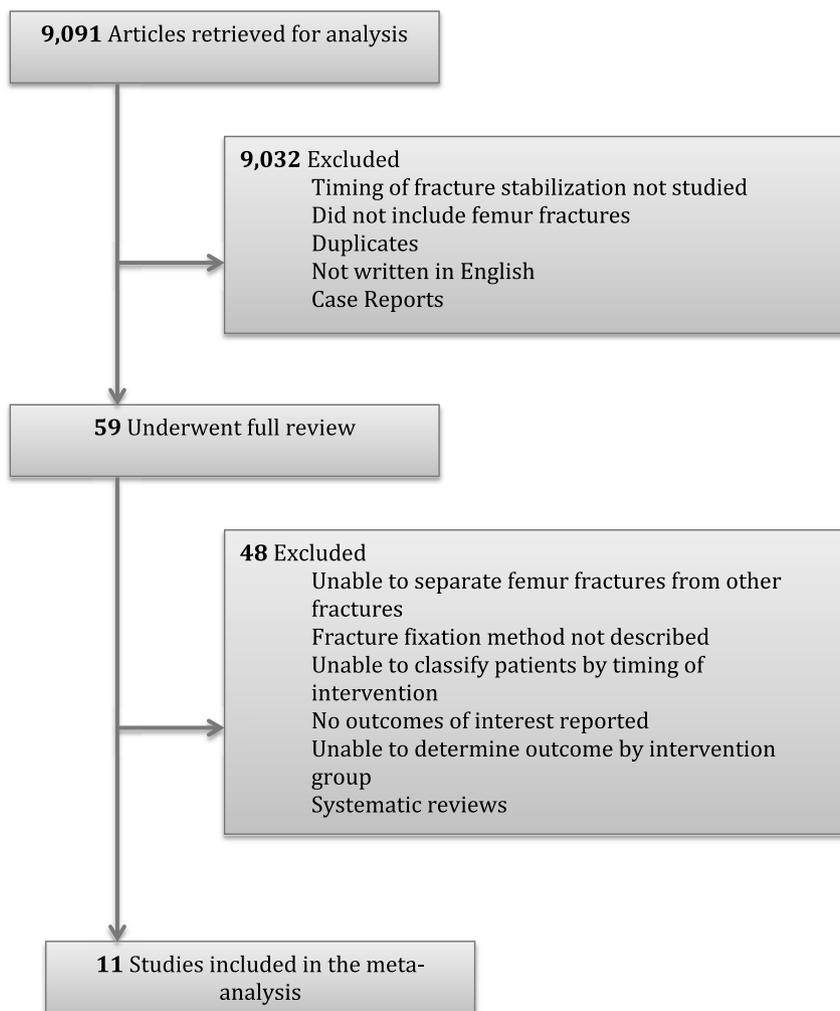


Figure 1. Flow diagram of included and excluded studies.

for all analyses. STATA 12.1 (College Station, TX) statistical analysis software was used for all statistical analyses.⁴³ There were not enough data to undertake meta-analysis for the other two outcomes (nonunion/malunion and amputations).

Assessment of Heterogeneity

Potential heterogeneity existed because of population differences, different types of surgery, and how patients were defined. We examined these differences across studies to assess clinical and methodological heterogeneity. For the meta-analysis, we used RevMan to calculate the I^2 statistic to determine the proportion of variation between studies attributable to heterogeneity, and variation was categorized as “low” ($I^2 = 25$ –49%), “moderate” ($I^2 = 50$ –74%), or “high” ($I^2 = 74$ –100%).

RESULTS

We retrieved 9,091 articles during the first phase of the literature search, of which 9,032 were excluded by duplicate removal and title review (Fig. 1). Fifty-nine articles addressing optimal timing of long bone fracture stabilization underwent

a full review to identify 11 studies comparing early (<24 hours) versus late (>24 hours) open reduction and internal fixation of femur fractures in trauma patients (Table 1). Of the 11 studies, 1 was a prospective randomized study⁵ and 10 were retrospective cohort studies.^{11,15,19,21–23,44–47} Across all studies, 7,189 patients were included, with 5,064 receiving early stabilization and 2,125 receiving late stabilization.

Participant Characteristics

The range of the mean ages in the studies reviewed was 18 years to 43 years. Most of the patients were men (61–78%). The mean Injury Severity Score (ISS) for patients receiving early stabilization ranged from 12 to 27, while patients receiving late stabilization ranged from 12 to 34 (Table 1).

RESULTS BY OUTCOME

Mortality

Eight studies reported the incidence of mortality,^{5,11,19,21–23,44,45} one of which was a prospective randomized study (Fig. 2).⁵ These studies included 6,930 patients (sample size

TABLE 1. Characteristics of Studies of Early Versus Late Internal Fixation of Femur Fracture Among Trauma Patients

Source	Design	No. Patients		Mean Age, y		Male Sex, %		Mean ISS	
		Early	Late	Early	Late	Early	Late	Early	Late
Bone et al., ⁵ 1989	PR	46	37	27	29	78	68	22	20
Brundage et al., ²² 2002	RO	867	214	28	30	70	70	17	19
Charash et al., ¹⁹ 1994	RO	105	33	31	30	NR	NR	12	28
Fakhry et al., ⁴⁴ 1994	RO	1,177	763	NR	NR	NR	NR	12	12
Morshed et al., ²³ 2009	RO	2,299	770	32	34	NR	NR	27	31
Nahm et al., ¹¹ 2011	RO	408	84	35	43	74	69	22	34
Pape et al., ¹⁵ 1993	RO	57	49	28	27	NR	NR	24	29
Reynolds et al., ⁴⁵ 1995	RO	35	70	33	33	74	64	27	33
Rogers et al., ⁴⁶ 1994	RO	18	49	37	38	61	69	NR	NR
Starr et al., ²¹ 1997	RO	12	10	38	33	NR	NR	27	26
van Niekerk et al., ⁴⁷ 1987	RO	40	46	18	19	75	74	NR	NR

NR, not reported; RO, retrospective observational; PR, prospective randomized.

range, 22–3,069). A meta-analysis of these eight studies showed no difference in mortality among patients with early stabilization compared with those undergoing late stabilization (RR, 0.74; 95% CI, 0.50–1.08; $p = 0.313$). Of note, the I^2 statistic was 15%, falling into the “low” heterogeneity category, indicating that the studies were comparable. In the only RCT, early internal fixation, there were only three total deaths (two in the early and one in the late cohort), which was not statistically significantly different.⁵

Infection

We included three studies reporting on infection and included 667 patients (sample size range, 68–492) (Fig. 3).^{11,15,46} A meta-analysis of these three studies showed no difference in infection between patients undergoing early surgery compared with those undergoing late surgery (RR, 0.40; 95% CI, 0.10–1.60; $p = 0.888$). The I^2 statistic was “low” at 0%, although

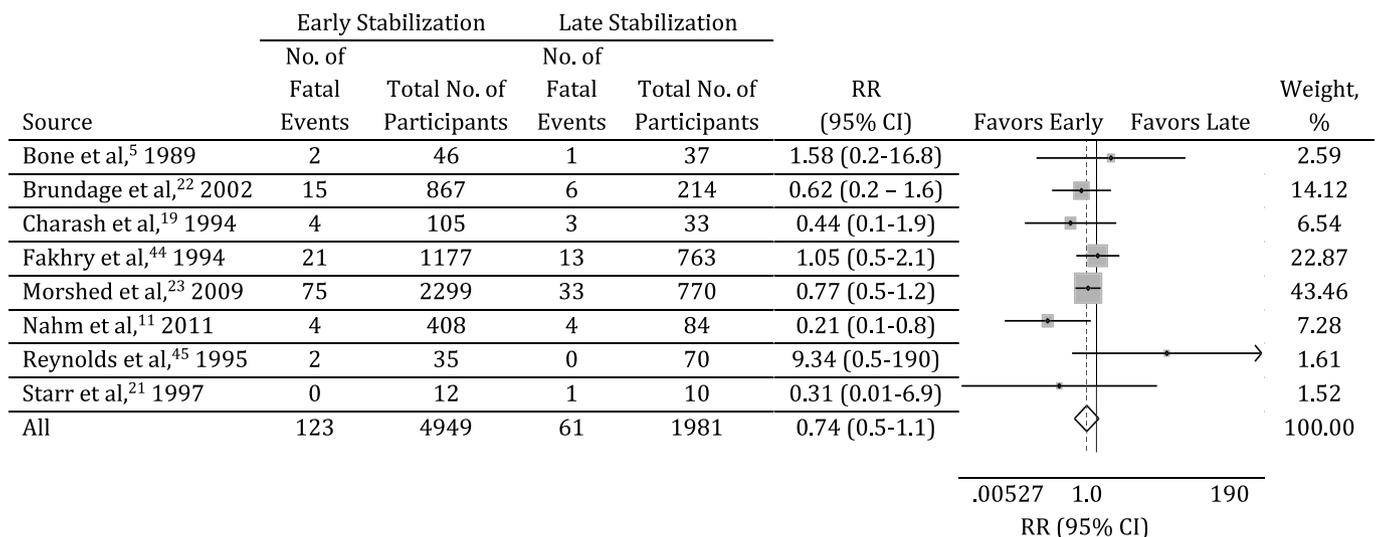
this is likely caused by the wide CIs of each study rather than a true homogeneity between the studies.

Venous Thromboembolism

We included six studies reporting on VTE and included 1967 patients (sample size range, 67–1,081),^{5,11,15,19,22,46} including the previously mentioned prospective randomized study (Fig. 4).⁵ A meta-analysis of these six studies showed no difference in VTE between patients undergoing early surgery compared with those undergoing late surgery (RR, 0.63; 95% CI, 0.37–1.07; $p = 0.896$). The I^2 statistic was “low” at 0%, although this is likely caused by the wide CIs of each study rather than a true homogeneity between the studies.

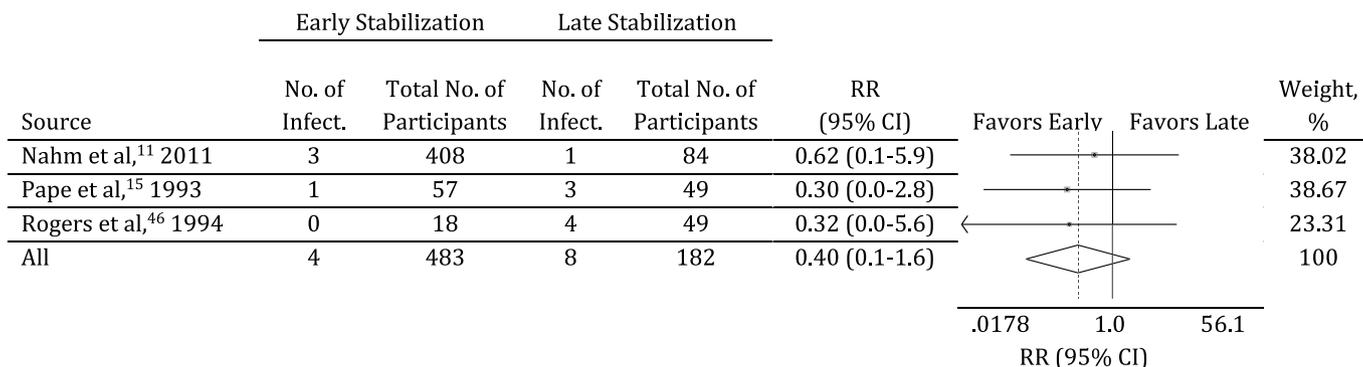
Nonunion/Malunion

Only one study reported nonunion/malunion outcomes, resulting in insufficient evidence to perform a meta-analysis for



Weights are calculated from random-effects analysis. Dashed line indicates the overall weighted point estimate (0.20); diamond, same overall weighted point estimate (95% CI). Shadow size varies relative to weight assigned to each study. Overall $I^2 = 14.9\%$ ($P = 0.313$).

Figure 2. Forest plot of RR of mortality with early (<24 hours) versus late (>24 hours) femur fracture stabilization in trauma patients.



Weights are calculated from random-effects analysis. Dashed line indicates the overall weighted point estimate (0.20); diamond, same overall weighted point estimate (95% CI). Shadow size varies relative to weight assigned to each study. Overall $I^2 = 0\%$ ($P = 0.888$).

Figure 3. Forest plot of RR of infection with early (<24 hours) versus late (>24 hours) femur fracture stabilization in trauma patients.

this outcome.⁴⁷ This study compared patients treated within 24 hours of their injury at their hospital with patients from another hospital who were treated greater than 24 hours after injury. They found delayed fixation resulted in more callus and more frequent secondary bone healing. In both patient groups, however, there were no nonunions or malunions reported.

Amputation

Only one study reported amputation outcomes, resulting in insufficient evidence to perform a meta-analysis for this outcome.¹⁵ This study retrospectively reviewed outcomes for multiple trauma patients with femoral shaft fractures based on the presence of additional severe thoracic injuries. Only two patients in each stabilization group (early vs. late) required amputation (early, 3.4%; late, 4.1%).

Grading the Evidence

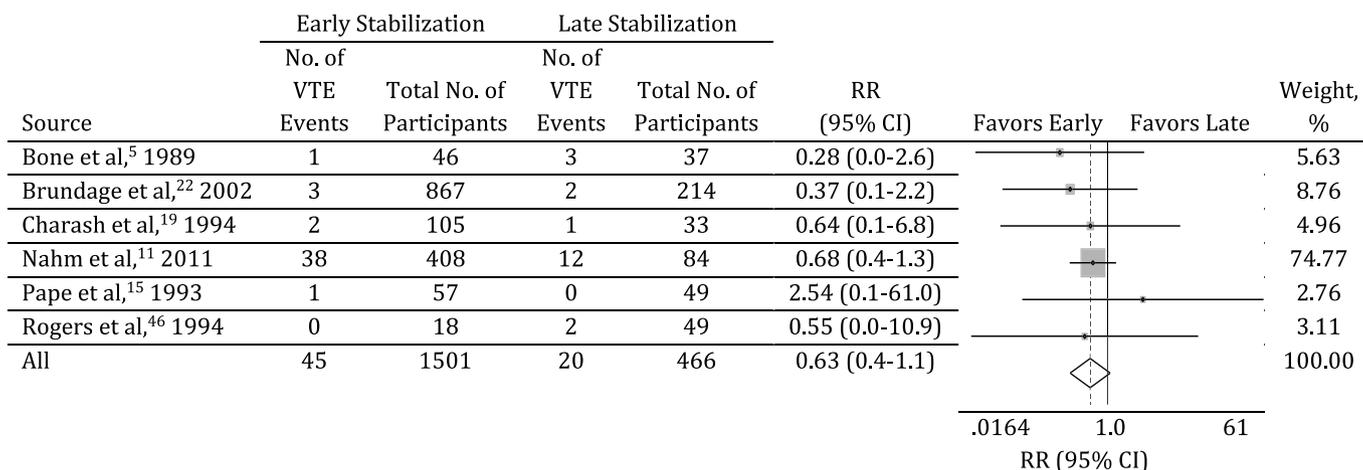
With the use of the GRADE framework for assessing all relevant outcomes, no serious risk of inconsistency or indirectness was found. However, moderate imprecision was noted

since the studies were small and CIs were large. We rated the prospective randomized study as having a moderate risk of bias, primarily based on study design.⁵ Among the retrospective studies, we rated only one study as having a moderate risk of bias²³ and the remainder as having a high risk of bias. Starting from observational studies (which are considered low quality), we did not rate up for the quality of evidence.

We rated the strength of evidence as low to support a reduction in mortality, infection, and VTE in trauma patients treated with early stabilization relative to late stabilization (Table 2). We rated the strength of evidence as insufficient to support any increase or decrease in nonunion/malunion or amputation in trauma patients treated with early stabilization relative to late stabilization (Table 3).

DISCUSSION

The findings of this study indicate that internal fixation of femur fractures in less than 24 hours after injury may be associated with a reduction in mortality, infection, and VTE.



Weights are calculated from random-effects analysis. Dashed line indicates the overall weighted point estimate (0.20); diamond, same overall weighted point estimate (95% CI). Shadow size varies relative to weight assigned to each study. Overall $I^2 = 0\%$ ($P = 0.896$).

Figure 4. Forest plot of RR of VTE with early (<24 hours) versus late (>24 hours) femur fracture stabilization in trauma patients.

TABLE 2. Strength of Evidence for Early (<24 Hours) Versus Late (>24 Hours) Stabilization of Femur Fractures in Trauma Patients

Outcome, Source	Risk of Bias	Strength of Evidence and Magnitude of Effect, %
Mortality		
		Low that early femur fracture stabilization is associated with lower incidence of mortality in trauma patients compared with late femur fracture stabilization; RR, 0.74 (95% CI, 0.50–1.08; $I^2 = 14.9\%$)
Bone et al., ⁵ 1989	Moderate	4.3 vs. 2.7
Brundage et al., ²² 2002	High	1.7 vs. 2.8
Charash et al., ¹⁹ 1994	High	3.8 vs. 9.1
Fakhry et al., ⁴⁴ 1994	High	1.8 vs. 1.7
Morshed et al., ²³ 2009	Moderate	3.3 vs. 4.3
Nahm et al., ¹¹ 2011	High	1.0 vs. 4.8
Reynolds et al., ⁴⁵ 1995	High	5.7 vs. 0
Starr et al., ²¹ 1997	High	0 vs. 10.0
Infection		
		Low that early femur fracture stabilization is associated with lower incidence of infection in trauma patients compared with late femur fracture stabilization; RR, 0.40 (95% CI, 0.10–1.60; $I^2 = 0\%$)
Nahm et al., ¹¹ 2011	High	0.7 vs. 1.2
Pape et al., ¹⁵ 1993	High	1.8 vs. 6.1
Rogers et al., ⁴⁶ 1994	High	0 vs. 8.2
Nonunion/Malunion		
		Insufficient that early femur fracture stabilization is associated with lower incidence of nonunion/malunion in trauma patients compared with late femur fracture stabilization.
van Niekerk et al., ⁴⁷ 1987	High	0 vs. 0
Amputation		
		Insufficient that early femur fracture stabilization is associated with lower incidence of amputation in trauma patients compared with late femur fracture stabilization.
Pape et al., ¹⁵ 1993	High	3.5 vs. 4.1
VTE		
		Low that early femur fracture stabilization is associated with lower incidence of VTE in trauma patients compared with late femur fracture stabilization; RR, 0.63 (95% CI, 0.37–1.07; $I^2 = 0\%$)
Bone et al., ⁵ 1989	Moderate	2.2 vs. 8.1
Brundage et al., ²² 2002	High	0.3 vs. 0.9
Charash et al., ¹⁹ 1994	High	1.9 vs. 3.0
Nahm et al., ¹¹ 2011	High	9.3 vs. 14.3
Pape et al., ¹⁵ 1993	High	1.8 vs. 0
Rogers et al., ⁴⁶ 1994	High	0 vs. 4.1

There was insufficient evidence to comment on the outcomes of amputation or nonunion/malunion. The studies reviewed did not separate outcomes of open from closed fractures. Hence, this recommendation applies to all femur fractures. Unlike the previous EAST PMG on long bone fractures, all other long bones, including tibia, were excluded from this analysis.

A major implication of this study is that early fracture fixation should be considered in all patients with femur fractures. In the absence of a clear contraindication to surgery or anesthesia, the recommendation of this review, although conditional, should prompt early fixation. However, the surgical decision must be individualized to each patient's needs. Delayed treatment has been associated with improved survival rates among patients with serious abdominal injuries and a reduction in adverse outcomes in patients with multiple injuries.¹³ In addition, delayed stabilization (24–48 hours) may be safer than stabilization within 12 hours for severely injured patients.⁴⁸

Of the large number of articles reviewed, there was only one prospective randomized trial addressing the issue of early versus late fixation of femur fractures.⁵ The total number of patients in this study (83) was relatively small. The only outcomes of interest with respect to this PMG were mortality and VTE. Among the other outcomes reported in this study, the early fixation arm had significantly shorter stay in the intensive care unit and in the hospital. As a result of the lower length of stay, the average hospital cost was also decreased in the early fixation arm.

The rest of the other articles reviewed were retrospective reviews. Hence, patients were not matched in early versus delayed fixation groups. Another issue was inconsistent timing of fracture fixation. In many articles, the time of fixation was less than 48 hours and not further specified. These were not included in the analysis. One article reported fixation less than 12 hours or greater than 48 hours.⁴⁹ Another article excluded all patients who had fixation after 48 hours. In addition, there were variations in the fracture type. We specifically excluded studies with intertrochanteric fracture fixation.⁵⁰ One article was excluded because patients with femur fractures were not separated from pelvis and spine fractures.⁵¹ Other articles were excluded as they compared the type of fixation, instead of the timing of fixation. Pediatric studies were also excluded. Finally, all case series with four or fewer cases were excluded.

Some of the articles reported damage-control orthopedics compared with definitive fixation. These articles had external fixation performed early, followed by definitive internal fixation later on. These articles were also excluded because their patients did not have internal fixation within 24 hours. Another major common reason for exclusion was that the outcomes reported were not relevant to this review, namely, mortality, infection, VTE, nonunion/malunion, and amputation. One of the items not considered was economics. However, it seems early fixation did lead to an efficient use of operating room and other resources compared with delayed fixation.^{5,46}

This PMG has several limitations primarily related to the study design resulting in a high risk of bias in all but two studies, resulting in a conditional recommendation. In addition, we were unable to separate open from closed femoral fractures. The findings are also limited to the five outcomes included in

TABLE 3. Outcomes Among Trauma Patients With Femur Fractures Who Received Early (<24 Hours) Versus Late (>24 Hours) Open Reduction and Internal Fixation

Study	No. Patients		Mortality		Infection		Nonunion/ Malunion		Amputation		VTE	
	Early	Late	Early	Late	Early	Late	Early	Late	Early	Late	Early	Late
Bone et al., ⁵ 1989	46	37	2	1	nr	nr	nr	nr	nr	nr	1	3
Brundage et al., ²² 2002	867	214	15	6	nr	nr	nr	nr	nr	nr	3	2
Charash et al., ¹⁹ 1994	105	33	4	3	nr	nr	nr	nr	nr	nr	2	1
Fakhry et al., ⁴⁴ 1994	1,177	763	21	13	nr	nr	nr	nr	nr	nr	nr	nr
Morshed et al., ²³ 2009	2,299	770	75	33	nr	nr	nr	nr	nr	nr	nr	nr
Nahm et al., ¹¹ 2011,	408	84	4	4	3	1	nr	nr	nr	nr	38	12
Pape et al., ¹⁵ 1993	57	49	nr	nr	1	3	nr	nr	2	2	1	0
Reynolds et al., ⁴⁵ 1995	35	70	2	0	nr	nr	nr	nr	nr	nr	nr	nr
Rogers et al., ⁴⁶ 1994	18	49	nr	nr	0	4	nr	nr	nr	nr	0	2
Starr et al., ²¹ 1997	12	10	0	1	nr	nr	nr	nr	nr	nr	nr	nr
van Niekerk et al., ⁴⁷ 1987	40	46	nr	nr	nr	nr	0	0	nr	nr	nr	nr

the literature review. No inference should be made about other outcomes such as fat embolism, compartment syndromes, and functional outcomes.

RECOMMENDATION

In trauma patients with open or closed femur fractures, we suggest early (<24 hours) open reduction and internal fracture fixation. This recommendation is conditional because the strength of the evidence is low. Early stabilization of femur fractures shows a trend (statistically insignificant) toward lower risk of infection, mortality, and VTE. Therefore, the panel concludes that the desirable effects of early femur fracture stabilization probably outweigh the undesirable effects in most patients. Additional well-designed observational or prospective cohort studies may be informative. Although the overall quality of evidence was low, the other factors GRADE allows the writing committee to consider helped to guide our recommendation. The potential patient benefit of early femur fixation likely outweighs the harm in most patients.

RECOMMENDATION: In trauma patients with open or closed femur fractures, we suggest early (<24 hours) open reduction and internal fracture fixation. This recommendation is conditional, and the strength of the evidence is low. Early stabilization of femur fractures shows a trend (statistically insignificant) toward lower risk of infection, mortality, and VTE. Therefore, the panel concludes that the desirable effects of early femur fracture stabilization probably outweigh the undesirable effects in most patients. Conditional recommendation (low quality of evidence).

USING THESE GUIDELINES IN CLINICAL PRACTICE

This guideline represents a very detailed summary of the literature regarding open reduction and internal fixation of femur fractures and surgical timing and is meant to inform the decision-making process, not replace clinical judgment. The optimal timing for internal fixation remains controversial.²⁻⁴

The literature available for review thus far support the course of earlier open reduction and internal fixation in polytrauma patients with open or closed femur fractures.

CONCLUSION

In conclusion, we conditionally recommend internal fixation of femur fractures in less than 24 hours from the time of injury to reduce mortality, infection, and VTE. Further research in a well-designed fashion with adequate sample size is needed to determine the benefits of early fixation of femur fractures.

AUTHORSHIP

R.R.G., S.S. and E.R.H. conceived the study. R.R.G. built the PICO questions. J.K.L., D.A., J.W., T.R., E.H., F.B.R., S.S., and R.R.G. voted regarding the outcomes of interest for the PICO questions. R.R.G., S.S., and T.L.O. evaluated the articles independently for outcomes and relevance. T.L.O. performed the entire literature search, read all the abstracts, and selected the articles for review. R.R.G., S.S., and T.L.O. reviewed and summarized those articles selected. T.L.O. extracted the data from those articles. E.R.H. and B.L. placed the extracted data in the RevMan and GRADEpro programs and evaluated the results for recommendations. R.R.G., S.S., and T.L.O. also evaluated the results for the recommendation. R.R.G., S.S., and T.L.O. wrote the manuscript. E.R.H. and B.L. contributed to the writing of the methods and results. All authors participated in the critical review of this article.

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DISCLOSURE

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