Timing of definitive treatment of femoral shaft fractures in patients with multiple injuries: A systematic review of randomized and nonrandomized trials

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BACKGROUND: Optimal timing of definitive treatment of femoral shaft fractures in patients with multiple injuries remains controversial. This study aimed to determine the impact of timing of definitive treatment (early, delayed, or damage-control orthopedics [DCO]) of femoral shaft fractures on the incidence of adult respiratory distress syndrome (ARDS), mortality rate, and hospital length of stay (LOS) in patients with multiple injuries.

METHODS: A systematic review of published English-language reports using MEDLINE (1946–2011), Embase (1947–2011), and Cochrane Library. Search terms included *femoral fractures*, *multiple trauma*, *fracture fixation*, and *time factors*. This study reviewed randomized and nonrandomized studies that (1) compared early and delayed treatment or early treatment and DCO and (2) reported the incidence of ARDS, mortality rate, or LOS. Extraction of articles was performed by one of the authors using predefined data fields.

RESULTS: Thirty-eight studies met our inclusion criteria. Studies were grouped into heterogeneous injuries with early versus delayed treatment (17 studies), heterogeneous injuries with early versus DCO (8 studies), head injury (13 studies), and chest injury (7 studies). Most of the studies (≥50%) reporting ARDS and mortality rate showed no difference in each of these groups. However, 6 of 7 and 2 of 3 studies reporting LOS in the heterogeneous injuries with early versus delayed and heterogeneous injuries with early versus DCO, respectively, showed shorter stay for early treatment. Pooled analyses were not conducted owing to changes in critical care delivery during the study period and variations in definitions of early treatment, ARDS, and multiple injuries. Thirty-five reports were based on nonrandomized trials and were subject to biases inherent in retrospective studies. The review process was limited by language and publication status.

CONCLUSION: The literature suggests that early definitive treatment may be used safely for most patients with multiple injuries. However, a subgroup of patients with multiple injuries may benefit from . (*J Trauma Acute Care Surg*. 2012;73: 1046–1063. Copyright © 2012 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE: Systematic review, level III.

KEY WORDS: Femoral fractures; multiple injuries; fracture fixation; adult respiratory distress syndrome; length of stay.

The timing of definitive fixation of femoral shaft fractures in patients with multiple injuries has been an area of interest for several decades. In the 1970s and 1980s, early total care (ETC) emerged as a treatment standard in which all orthopedic injuries were definitively stabilized on an early basis. Several studies demonstrated that early treatment reduced pulmonary complications, mortality, and hospital length of stay (LOS).[1–10]

During the 1990s, studies questioned the use of ETC in chest or head injury. Increased morbidity following early surgery in these patients was explained by the two-hit hypothesis.[11] Investigators proposed that a traumatic event (first hit) followed by early surgery (second hit) may lead to an overwhelming inflammatory response, ultimately culminating in acute respiratory distress syndrome (ARDS) or multiple-organ failure (MOF).[12–16] In an effort to minimize early surgery, Scalea et al.[17] proposed damage-control orthopedics (DCO). Proponents of DCO suggest that external fixation provides the benefits of early skeletal stability but reduces the second hit of surgery by minimizing blood loss and anesthesia time.[18,19]

Systematic reviews were previously undertaken to determine the appropriate timing of femoral fracture treatment in patients with multiple injuries.[20,21] These reviews concluded that the evidence does not support a specific strategy. Since then, a randomized, prospective study,[22,23] and numerous other retrospective studies have been published, warranting another analysis of the literature. We examined the impact of timing of femoral shaft fracture treatment in skeletally mature patients with multiple injuries on the incidence of ARDS, in-hospital mortality rate, and LOS by reviewing these studies as well as previous randomized and nonrandomized studies.

MATERIALS AND METHODS

Studies were limited to published reports comparing early and delayed treatment or DCO in patients with multiple injuries.[10,22,24] Furthermore, pediatric patients were excluded because multiple-injury and fracture surgery may have different effects on in-hospital complications compared with those of adults.[25] Among potential outcomes to report in this review, mortality was of interest owing to its reliability as an outcome across different studies. ARDS was chosen because of its role in the inflammatory response following trauma and fracture surgery.[12–16] Finally, LOS has important economic and organizational implications for trauma centers.[26,27]

A search of MEDLINE (1946 to May 3, 2011), Embase (1947 to May 7, 2011), and Cochrane Library databases (May 28, 2011) was performed. Searches were limited to human studies published in the English language. The following medical subject headings (MeSH) and search strategies were used for the MEDLINE search: *femoral fractures* [MeSH] AND *multiple trauma* [MeSH] NOT *femoral neck fractures* [MeSH] NOT *hip fractures* [MeSH]; *femoral fractures* [MeSH] AND *fracture fixation* [MeSH] NOT *femoral neck fractures* [MeSH] NOT *hip fractures* [MeSH]; *femoral fractures* [MeSH] AND *time factors* [MeSH] NOT *femoral neck fractures* [MeSH] NOT *hip fractures* [MeSH]; *multiple trauma* [MeSH] AND *fracture fixation* [MeSH]; *multiple trauma* [MeSH] AND *time factors* [MeSH]; and *fracture fixation* [MeSH] AND *time factors* [MeSH]. Comparable search strategies were conducted in Embase and the Cochrane Library. Furthermore, bibliographies of included reports were searched manually. Eligibility assessment was conducted in an unblinded manner by one reviewer.

We generated a data extraction sheet. One of the authors used this data extraction sheet to analyze studies for the data points (study design, number of patients in the treatment groups, the number of femoral shaft fractures, injury profile of the patients, and outcomes), and the other author checked the extracted data. Mean values were reported unless otherwise noted. Statistical significance was determined by $p < 0.05$. If p values were not reported in the reference, they were calculated with Fisher's exact test for categorical variables and

Student's *t* test for continuous variables, if possible. A systematic assessment of risk of bias within and across studies was not conducted because most of the reports (35 of 38) were retrospective.

The references were organized into four groups based on associated injury and compared within each group: heterogeneous injuries with early versus delayed treatment, heterogeneous injuries with early treatment versus DCO, head injury, or chest injury. Studies with patient populations that were not stratified into subgroups defined by specified nonmusculoskeletal injury were placed into the heterogeneous injuries group. Summary measures were reported as incidence of ARDS, mortality rate, and LOS as a mean in days. Study results were not combined for a pooled analysis. No external funding was provided for this project.

RESULTS

The MEDLINE, Embase, and Cochrane Library inquiries yielded 5,071; 2,185; and 114 search results, respectively (Fig. 1). References were excluded for reasons as listed. A total of 38 references were included. Because patient inclusion criteria, timing of intervention, and outcomes varied markedly, we focused on describing the studies, results, conclusions, and limitations and on qualitative synthesis instead of meta-analysis.

Heterogeneous Injuries With Early Versus Delayed Treatment

One prospective randomized study[10] and 16 retrospective studies were analyzed (Table 1). Eight studies reported incidence of ARDS, 14 studies reported mortality rate, and 10 studies

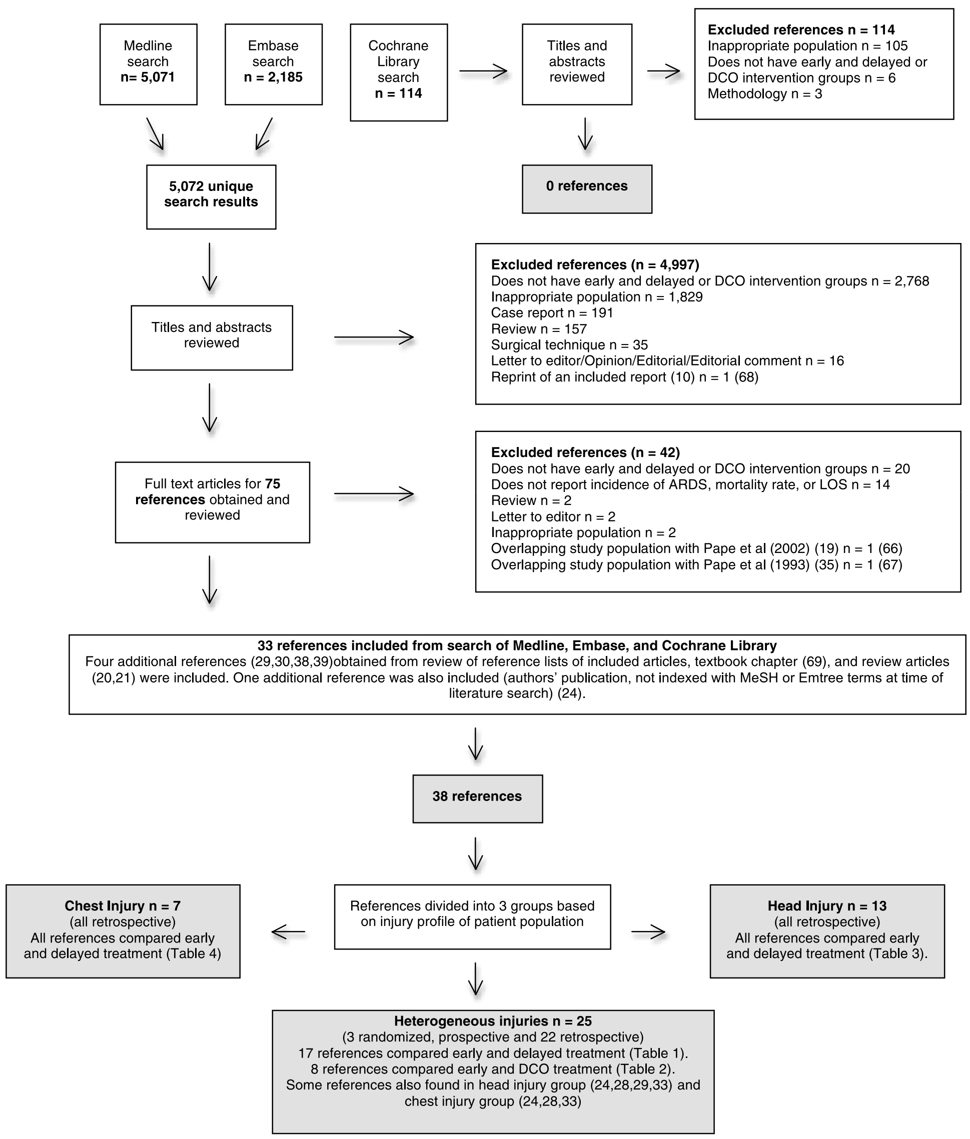

Figure 1. Systematic literature review process. Literature search of MEDLINE, Embase, and Cochrane Library database yielded 38 total references. Reasons for exclusion of references are provided. Note that ''inappropriate population'' refers to studies that do not include skeletally mature patients with multiple injuries with femoral shaft fractures and focus on injuries to other anatomic locations, low-energy trauma, pathologic fractures, or skeletally immature patients.

TABLE 1. References Comparing Early and Delayed Treatment in Patients with Heterogeneous Injuries

Reference	Only Femoral Shaft Fractures Included?	Time Points			Outcomes			Conclusion
			Early	Delayed		Early	Delayed	
Goris et al. (1982)[4]	No, included the femur, tibia, humerus, radius, and ulna (68 femur fractures)		≤24 h	>24 h	*ARDS, %*	17.4	75.0*	Early treatment: ↓ ARDS and mortality
		n	46	12	*Mortality, %*	2.2	10.9*	
		HTI-ISS	37.7	54.6†	*Vent, d*	2.5	10†	
		HTI Chest ≥ 3, %	23.9	75.0*				
					Note: Vent (days) is mean value for survivors only.			
Talucci et al. (1983)[8]	Yes		≤24 h	5–24 d	*FES, %*	0	11*	Early treatment: ↓ FES; no difference in ARDS
		n	57	43	*ARDS, %*	7	5	
		ISS	23.2	12.4*				
Johnson et al. (1985)[5]	No, included the femur, tibia, humerus, radius, ulna, spine, and pelvis (113 femur fractures)		≤24 h	>24 h	*ARDS, %*	7.2	38.8*	Early treatment: ↓ ARDS; no difference in mortality
		n	83	49	*Mortality, %*	2.4	12.2	
		ISS	38.2	38.0	*Vent, d*	4.9	11.1†	
					LOS, d	31.6	38.3†	
Seibel et al. (1985)[6]	No, included the femur and acetabulum		Immediate	Delayed	*Vent, d*	3.4	9.7[a]* and 21[b]*	Early treatment: ↓ LOS
		n	20	20[a] and 9[b]				
		Mean time to fixation, d	NR	10[a] and 30[b]	*LOS, d*	23	45[a]* and 61[b]*	
		HTI-ISS	36.3	37.3[a] and 29.3[b]				
		Note: Patients in the immediate group stabilized on night of admission (average time to stabilization NR); statistical differences are relative to early group. [a]Stabilized 10 d after admission (mean); [b]Stabilized 30 d after admission (mean).						
Eriksson and Wallin (1986)[9]	Yes		≤12 h	>12 h	*PE, %*	0	2.1	No difference in mortality or LOS
		n	20	47	*Mortality, %*	0	0	
					LOS, d	36.4	39.9†	
Broos et al. (1987)[7]	No, included the femur, tibia, humerus, radius, ulna, and pelvis		Early	Delayed	*Mortality, %*	4.8	6.5	No difference in mortality
		n	104	230				
		HTI-ISS	39.2	39†				
		Note: 82% of fractures in early group treated ≤24 h and 52% of fractures in delayed group treated >24 h.						
Bone et al. (1989)[10]‡	Yes		≤24 h	>48 h	*FES, %*	0.0	5.4	Early treatment: ↓ ARDS and LOS; no difference in mortality
		n (ISS ≥ 18)	46	37	*Pneumonia, %*	2.2	16.2*	
		ISS	31.8	31.3	*ARDS, %*	2.2	16.2*	
					Mortality, %	4.3	2.7	
					ICU, d	2.8	7.6*	
					LOS, d	17.3	26.6*	

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TABLE 1. *(Continued)*

Reference	Only Femoral Shaft Fractures Included?	Time Points			Outcomes			Conclusion
			Early	Delayed		Early	Delayed	
Beckman et al. (1989)[28]	No, included the femur, tibia, and humerus		≤48 h	>48 h	*PE, %*	0.0	7.7	Early treatment: ↓ pulmonary complications; no difference in ARDS, mortality, or LOS
		n	19	78	*FES, %*	0.0	10.3	
		ISS	33	31	*ARDS, %*	0.0	2.6	
					Pulmonary complication, %	0.0	19*	
					Mortality, %	5.3	2.8	
					Vent, median, d	0	0	
					LOS, median, d	20	25	
					Note: Pulmonary complication is FES, PE, or ARDS.			
Behrman et al. (1990)[29]	Yes		≤48 h	>48 h	*Increased pulmonary shunt (all patients)*	NR	NR*	Early treatment: ↓ LOS
		n	121	218				
		ISS	13.5	15.3				
					ARDS (n)	0^a and 0^b	2^a and 5^b	
					ICU (ISS > 35), d	3	8*	
					LOS (all patients), d	17	24*	
		Note: [a]ISS 16–35, n = 104 (n in early and delayed, NR); [b]ISS >35, n = 33 (n in early and delayed, NR).						
Sutcliffe (1994)[30]	No, types of fracture not specified (no. femur fractures not specified)		≤48 h	>48 h	*Mortality, %*	20.2	29.7	No difference in mortality
		n	99	101				
Fakhry et al. (1994)[31]§‖	Yes		≤1 d	>1 d	*Mortality, %*	3.8	1.7	No difference in mortality
		n (ISS ≥ 15)	212	120	*LOS, d*	18.4	22.2†	
		ISS	23	22†				
Bone et al. (1994)[32]§	No, included the femur, pelvis, acetabulum, bilateral tibia, or tibia and additional fracture		≤48 h	Delayed	*Mortality, %*	12.0	19.3*	Early treatment: ↓ mortality
		n (ISS ≥ 18)	676	906				
		Note: Delayed group composed of patients from ACS Multiple Trauma Outcome Study database, who were assumed to undergo delayed treatment (actual time to treatment unknown).						

Reynolds et al. (1995)[33]	Yes		≤24 h	>24 h	*Mortality, %*	5.7	0.0[a] and 0.0[b]	Early treatment: ↓ in LOS; no difference in mortality
		n (ISS ≥ 18)	35	13[a] and 57[b]				
		ISS	27.4	25.2[a] and 34.4[b]*	*Vent, d*	4.9	13.0[a] and 7.1[b]	
		GCS	13.3	14.8[a] and 8.6[b]*				
		AIS Head	1.97	1.92[a] and 2.36[b]*	*LOS, d*	13.7	17.3[a] and 21.9[b]*	
		AIS Chest	2.11	1.77[a] and 2.07[b]				
		[a]24–48 h; [b]>48 h Note: All significant differences are between ≤24-h and >48-h groups.						
Brundage et al. (2002)[34]§‖	Yes		≤24 h	>24 h	*Pneumonia, %*	15	24,[a] 35,[b]* and 13[c]	Early treatment: ↓ ARDS and LOS; no difference in mortality
		n (ISS > 15)	399	79[a], 23[b], 15[c]				
		ISS	25.08	26.09[a] 28.13[b] 27.67[c]	*ARDS, %*	7.8	14,[a] 39,[b]* and 6.7[c]	
		AIS head	2.03	2.46[a], 2.09[b], 3.00[c]†	*Mortality, %*	3.8	6.3,[a] 0.0,[b] and 6.7[c]	
		AIS chest	1.55	1.62[a], 1.69[b], 1.58[c]	*ICU, d*	7.03	7.98,[a] 26.2,[b]* and 8.20[c]	
					LOS, d	13.7	15.5,[a] 31.0,[b]* and 13.2[c]	
		[a]>24–48 h; [b]>48–120 h; >120 h Note: *p* values are calculated relative to the early group.						
Morshed et al. (2009)[35]	Yes		≤12 h	>12 h	*Mortality, %*	3.7	1.9,[a] 4.2,[b] 4.4,[c] and 4.3[d]	>12–24 h: ↓ mortality
		n	1759	540[a], 359[b], 272[c], 139[d]	*Crude relative risk for mortality*	—	0.50,[a] 1.13,[b] 1.19,[c] and 1.17[d]	
		NISS[e]	27.35	27.21[a] 29.20[b] 32.31[c] 34.68[d]				
		GCS[e]	12.67	12.69[a] 11.66[b] 10.77[c] 9.68[d]	*IPTW relative risk for mortality*	—	0.45,[a]* 0.83,[b] 0.58,[c]* and 0.43[d]*	
		[e]Significant ($p < 0.001$) association with treatment. [a]>12–24 h; [b]>24–48 h; [c]>48–120 h; [d]>120 h Note: All significant differences are relative to the ≤12-h group; relative risk calculated in reference to ≤12-h group						
Lefaivre et al. (2010)[36]	Yes		<8 h	≥8 h	ARDS, %	1.39	1.31[a] and 1.84[b]	≥8–24 h: ↓ mortality
		n	1437	304[a], 217[b]				
		Note: Time points refer to arrival in ED to arrival in operating room for either ETC or DCO			OR ARDS	—	0.867[a] and 1.537[b]	
					Mortality, %	10.79	1.32[a]* and 5.99[b]*	
					OR Mortality	—	0.140[a]* and 0.413[b]	
		[a]≥8–24 h, [b]>24 h						

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TABLE 1. (Continued)

Reference	Only Femoral Shaft Fractures Included?	Time Points	Early	Delayed	Outcomes	Early	Delayed	Conclusion
		Note: OR is calculated in reference to <8-h group; mortality rate is lowest ($p < 0.05$) in ≥8–24-h group						
Nahm et al. (2011)[24]§‖	No, included intertrochanteric and femoral neck fractures (455 femoral shaft fractures)		≤24 h	>24 h	*PE, %*	0.0	1.7	Early treatment: ↓ mortality and LOS; no difference in ARDS
		n (ISS ≥ 18)	408	84	*Pneumonia, %*	9.8	22.6	
		ISS	28.8	36.4*	*ARDS, %*	1.7	4.8	
		GCS ≤ 8, %	10.8	26.2*	*Sepsis, %*	1.0	9.5*	
		AIS chest ≥ 3, %	29.9	58.3*	*MOF, %*	1.2	6.0*	
					Mortality, %	1.0	4.8*	
					Vent, d	3.2	9.8*	
					LOS, d	10.6	18.5*	

*$p < 0.05$.
†*p* value could not be determined.
‡Prospective, randomized study.
§Reference also included in Table 5.
‖Reference also included in Table 7.
↓, decreases; ↑, increases; ACS, American College of Surgeons; ED, emergency department; FES, fat embolism syndrome; HTI, hospital trauma index; ICU, intensive care unit length of stay; IPTW, inverse probability of treatment weight; ISS, Injury Severity Score; NISS, new Injury Severity Score; NR: not reported; OR, odds ratio; PE, pulmonary embolism; Vent, length of time on mechanical ventilation.

TABLE 2. Heterogeneous Injuries With Early versus Delayed (17 Studies)

	References Reporting	Early Definitive Treatment	Delayed Definitive Treatment	No Difference
ARDS	47.1% (8/17)	50.0% (4/8)[4,5,10,34]	0% (0/8)	50.0% (4/8)
Mortality rate	82.4% (14/17)	21.4% (3/14)[4,24,32]	7.1% (1/14)[36]	71.4% (10/14)
LOS	41.2% (7/17)*	85.7% (6/7)[6,10,24,29,33,34]	0% (0/7)	14.3% (1/7)

**p* values could not be determined for three references,[5,9,31] which are not included.

reported LOS (Table 2). Four studies found a lower incidence of ARDS with early treatment (≤24 hours) compared with delayed treatment (>24 hours or >48–120 hours).[4,5,34] Four references indicated no difference in ARDS between early- and delayed-treatment groups. Three references reported a lower mortality rate with early treatment (≤24 hours or ≤48 hours after injury) compared with delayed treatment.[4,24,32] In another study, Lefaivre et al.[36] reported increased mortality with surgery less than 8 hours after arrival compared with 8 or longer to 24 hours or longer than 24 hours. Ten references reported no difference in mortality between early- and delayed-treatment groups. Finally, six studies demonstrated shorter stay with early treatment (up to within 48 hours after injury) compared with delayed treatment (range, >48 hours to 30 days).[6,10,24,29,33],[34] One study detected no difference in LOS between early and delayed treatment. Although statistical analyses could not be performed with data provided in three references,[5,9,31] the trend indicated shorter stay with early treatment (≤12 or 24 hours) as compared with delayed treatment (>12 or 24 hours).

Heterogeneous Injuries With Early Treatment Versus DCO

Two prospective, randomized reports[22,23] and six retrospective studies investigating early treatment versus DCO for patients with heterogeneous injuries were reviewed (Table 3). Six studies reported incidence of ARDS, four studies reported mortality rate, and four studies reported LOS (Table 4). One study reported a higher incidence of ARDS with early treatment (≤4 days) compared with DCO,[50] while five references indicated no difference between early (≤8 or 24 hours) and DCO groups. Two references reported a lower mortality rate with early treatment (≤24 hours) compared with DCO.[17,53] Two references reported no difference in mortality between early (≤4 days or ≤24 hours) and DCO groups. Two studies reported shorter stay with early treatment (≤24 hours) compared with DCO.[17,54]

Head Injury

All 13 studies were retrospective in design (Table 5). Five references reported the incidence of ARDS, all references reported mortality rate, and eight studies reported LOS (Table 6). Brundage et al.[34] found a lower incidence of ARDS for patients treated within 24 hours of injury compared with patients treated between 48 and 120 hours of injury. Four other references found no difference in the incidence of

TABLE 3. References Comparing Early Treatment and DCO in Patients with Heterogeneous Injuries

Reference	Only Femoral Shaft Fractures Included?	Time Points			Outcomes			Conclusions
			Early	DCO		Early	DCO	
Friedl et al. (1996)[50]	No, included the femur and tibia		≤4 d	DCO	*ARDS, %*	25.0	0.0*	DCO: ↓ ARDS; no difference in mortality
		n	32	23	*Mortality, %*	12.5	0.0	
		ISS	21.4	41.8*				
Scalea et al. (2000)[17]	Yes		Primary IMN	DCO	*Mortality, %*	<1	9*	Early treatment: ↓ mortality and LOS
					ICU (if > 0), median, d	8.0	11.0	
		n	281	43				
		ISS	16.8	26.8*				
		GCS	14.2	11.0*	*LOS, median, d*	5.7	17.5*	
		AIS head ≥ 3, %	15	56*				
Pape et al. (2002)[19]	Yes		≤8 h	DCO	*ARDS, %*[51]	15.1%	9.1%	No difference in ARDS
		n	386	128	*MOF, %*	28.2%	32.4%	
		ISS	36.9	39.4†	*LOS, d*	14.2	14.1†	
		AIS head	2.2	2.9†				
		AIS chest	3.2	3.9†				
Pape et al. (2003)[23]‡	No, included long bone shaft fractures of the lower extremities		≤24 h	DCO	*Pneumonia, %*	5.9%	5.6%	No difference in ARDS
		n	17	18	*ARDS, %*	0.0	0.0	
		ISS	21.7	23.2	*Sepsis, %*	0.0	0.0	
		GCS	14.4	12.9	*ICU, d*	4.8	3.3	
		AIS head	2.0	2.0				
		AIS chest	2.2	2.5				
Pape et al. (2007)[22]‡	Yes		<24 h	DCO	*ALI, %*	12.9[a] and 52.4[b]	28.6[a] and 16.7[b]*	Early treatment: ↓ vent time in stable pts and ↑ ALI in borderline pts
		n	71[a], 23[b]	50[a], 21[b]				
		ISS	23.33	29.04*	*ARDS, %*	6.3[a] and 16.7[b]	9.5[a] and 11.1[b]	
		AIS head	1.09	1.83*				
		AIS chest	1.87	2.21	*Sepsis, %*	6.3[a] and 36.8[b]	11.9[a] and 11.1[b]	
		Note: Injury profile was not reported for borderline and stable patients stratified into <24-h and DCO groups			*MOF, %*	0.0[a] 22.2[b]	0.0[a] and 16.7[b]	
					Vent, d	2.8[a] and 16.6[b]	5.9[a] and 15.0[b]*	
				[a]Stable; [b]borderline[20,21]				
Tuttle et al. (2009)[52]	Yes		≤24 h	DCO	*ARDS score*	1.81	1.79	No difference in ARDS score and LOS
		n	42	55				
		ISS	36.8	39.1	*MOF score*	2.78	3.08	
					Vent, d	11.4	10.8	
					LOS, d	20.9	17.2	

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TABLE 3. *(Continued)*

Reference	Only Femoral Shaft Fractures Included?	Time Points			Outcomes			Conclusions
			Early	*DCO*		*Early*	*DCO*	
O'Toole et al. (2009)[53]	Yes		Primary IMN	DCO	*ARDS, %*	1.5	0.0	Early treatment: ↓ mortality
					Mortality, %	2.0	17.9*	
		n	199	28	*ICU, d*	7.1	17.3*	
		ISS	27.4	36.2*				
		AIS head > 2, %	28.1	39.3				
		AIS chest > 2, %	75.9	85.7				
		Average time to IMN/exfix, h	14.0	13.0				
Scannell et al. (2010)[54]	Yes		≤24 h	DCO	*PE, %*	2.4	0.0^{a} and 0.0^{b}	Early treatment: ↓LOS; no difference in ARDS or mortality
		n	126	19^{a} and 60^{b}				
		ISS	23.8	$27.4^{a,c}$ and $29.4^{b,d}$	*Pneumonia, %*	11.9	36.8^{a} and $43.3^{b,d}$	
		GCS	12.8	$9.5^{a,c}$ and $8.4^{b,d}$				
		AIS head/neck	1.2	1.0^{a}, and $2.5^{b,d,e}$	*ARDS, %*	4.0	5.3^{a} and 5.0^{b}	
		AIS chest	2.4	1.8^{a} and 2.0^{b}				
		Average time to IMN/DCO, h	10.8	6.6^{a} and NR^{b}	*Sepsis, %*	6.3	$31.6^{a,c}$ and 8.3^{b}*	
		Average time to definitive IMN, d	—	5.0^{a} and 4.1^{b}	*MOF, %*	14.3	$63.2^{a,c}$ and $38.3^{b,d}$	
					Mortality, %	0.8	0.0^{a} and 5.0^{b}	
					Vent (if > 0), d	11.0	15.5^{a} and 17.3^{b}	
					LOS, d	12.9	$36.2^{a,c}$ and $26.5^{b,d,e}$	

[a] Exfix; [b] Skeletal traction

[c] $p < 0.05$ between early group and exfix groups

[d] $p < 0.05$ between early group and skeletal traction groups

[e] $p < 0.05$ between exfix and skeletal traction groups

*$p < 0.05$.

†p value could not be determined.

‡Prospective, randomized study.

↓, decreases; ↑, increases; ALI, acute lung injury; exfix, external fixation; ICU, intensive care unit length of stay; IMN, intramedullary nailing; ISS, Injury Severity Score; LOS, hospital length of stay; NR; not reported; PE, pulmonary embolism; Vent, length of time on mechanical ventilation.

TABLE 4. Heterogeneous Injuries With Early versus DCO (Eight Studies)

	References Reporting	Early Definitive Treatment	DCO	No Difference
ARDS	75.0% (6/8)	0.0% (0/6)	16.7% (1/6)[50]	83.3% (5/6)
Mortality rate	50.0% (4/8)	50.0% (2/4)[17,53]	0.0% (0/4)	50.0% (2/4)
LOS	37.5% (3/8)*	66.7% (2/3)[17,54]	0.0% (0/3)	33.3% (1/3)

**p* value could not be determined for 1 reference[19] which is not included.

ARDS between early (≤24 hours) and delayed (>24 hours) groups. Two references reported decreased mortality for patients treated early (≤24 or 48 hours) compared with those with delayed treatment.[32,38] Eleven references reported no difference in mortality between early (≤12 or 24 hours) and delayed (>24 or ≥96 hours) treatment. In regard to LOS, six references reported no difference between early and delayed treatment. Two references reporting LOS without statistical analyses suggested a trend toward shorter stay with early treatment (≤24 hours) compared with delayed treatment (>24 hours).[31,34]

Chest Injury

Seven retrospective studies investigating patients with chest injuries were reviewed (Table 7). Among the five references reporting incidence of ARDS, one reference reported less ARDS for patients (chest Abbreviated Injury Scale [AIS] score ≥ 3) treated within 24 hours of injury compared with patients treated between 48 and 120 hours of injury (Table 8).[34] In contrast, another reference demonstrated increased ARDS with early treatment (≤24 hours) compared with delayed treatment (>24 hours) for patients with chest AIS score of 2 or greater.[47] Three other studies demonstrated no difference in ARDS between early (≤24 hours) and delayed (>24 hours) treatment. Six references reported mortality rate; all reported no difference in mortality between early (≤24 or 48 hours) and delayed (>24 or 48 hours) treatment groups. Finally, of the three references reporting LOS, one reference noted a shorter stay among patients treated within 24 hours of injury compared with patients treated between 48 and 120 hours.[34] Two other references demonstrated a trend toward decreased LOS for patients treated within 24 hours of injury.

DISCUSSION

The evidence for the effect of timing of definitive treatment of femoral shaft fractures is mainly inconclusive with many studies showing no difference for ARDS, mortality, and LOS (Tables 2, 4, 6, and 8). However, most of the studies reporting LOS in the heterogeneous injuries group demonstrated a significantly lower LOS for early treatment compared with delayed treatment or DCO. Furthermore, among studies showing a difference in ARDS and mortality, the majority favored early treatment compared with delayed treatment or DCO. Exceptions in the heterogeneous injuries group include one study showing more mortality with surgery after less than 8 hours of arrival as compared with 8 hours or longer to 24 hours or longer than 24 hours[36] and another study showing less ARDS with DCO compared with early treatment (≤4 days).[50] Exceptions in the chest injury group include one reference showing decreased incidence of ARDS with delayed treatment (>24 hours) for patients with chest injury (chest AIS score ≥ 2).[47]

Our findings are consistent with two previous reviews. Dunham et al.[21] compared early and delayed treatment of long-bone fractures in patients with multiple injuries and showed potential benefit of early treatment on the incidence of ARDS and LOS for patients with mixed injury. No benefit was shown for early treatment on mortality. In a more recent review, Rixen et al.[20] found a nonsignificant overall odds ratio of 0.89 for mortality associated with early treatment. They concluded that there is no definite benefit or harm for early treatment, even in subgroups of patients with head and/or chest injury. A third review published in 2001 by Robinson[55] demonstrated a relative risk reduction for pulmonary complications of 68% for early treatment compared with delayed or nonoperative treatment. However, this report did not provide methodology on how studies were selected for analysis and is difficult to compare with the results of this review.

Outcomes

The reported incidence of ARDS among included studies varied. The European Polytrauma Study on the Management of Femur Fractures group performed a randomized European multicenter study. Among "borderline" patients, the incidence of ARDS was 16.7% in early treatment (≤24 hours) and 11.1% in DCO (p = 0.618).[22] "Borderline" patients were more severely injured as defined by criteria outlined by the same group of authors.[56,57] Of note, the authors used the definition of ARDS put forth by the American European Consensus Conference (AECC).[58] Compared with European studies, North American studies tended to report a lower incidence of ARDS.[53] In a recent North American retrospective study using the AECC definition of ARDS, O'Toole et al.[53] reported an incidence of ARDS of 1.5% for patients treated on an early basis and 0.0% for patients treated with DCO (p = 1.000).

Reasons for the range in the incidence of ARDS may be multifactorial. First, the definitions used for ARDS were not consistent across studies. However, this reason did not account for the difference found in the European Polytrauma Study on the Management of Femur Fractures randomized study[22] and the 2009 retrospective study of O'Toole et al.[53] because both used the same AECC definition but had significantly different overall incidence of ARDS (1.3% [3 of 227] in the study of O'Toole et al. and 9.7% [16 of 165] in the study of Pape et al.;[22] $p < 0.001$). This finding may suggest a difference between European and North American studies. European and North American trauma centers may have different protocols for preoperative resuscitation. For example, in a 2002 retrospective study conducted in Germany, patients underwent fracture surgery within 8 hours of injury, limiting the amount of resuscitation performed before surgery. In contrast, O'Toole et al.

TABLE 5. References Comparing Early and Delayed Treatment in Patients with Head Injury

Reference	Only Femoral Shaft Fractures Included?	Time Points			Outcomes			Conclusion
			Early	Delayed		Early	Delayed	
Kotwica et al. (1990)[37]	No, included pelvic or lower extremity fracture (27 femoral fractures)		≤12 h	4–10 d	*Mortality, %*	13.7	22.4	No difference in mortality
		n	51	49				
		GCS ≤ *9, %*	52.9	51.0	Note: GOS data reported but contradicted mortality data; only mortality data reported in this table.			
Hofman and Goris (1991)[38]	No, included unstable vertebral, pelvic, femur, or type II or III open tibia fracture		≤24 h	>24 h	*GOS 3–5*	73	47	Early treatment: ↓ mortality
		n	15	43	*ICU, d*	19	9	
		ISS	44	36*	*Mortality, %*	13.3	46.5*	
		GCS	4.6	4.7				
		Note: Delayed group includes patients with no major fracture (number not specified).						
Poole et al. (1992)[39]	No, included femoral neck or shaft or tibial shaft fracture		≤24 h	>24 h	*PE, %*	2.2	3.8	No difference in mortality or ARDS
		n	46	26	*FES, %*	2.2	3.8	
		ISS	27.6	33.9	*Pneumonia, %*	15.2	3.8	
		GCS	12.0	10.1	*ARDS, %*	4.3	7.7	
					Mortality, %	4.3	0.0	
Fakhry et al. (1994)[31]†‡	Yes		≤1 d	>1 d	*Mortality, %*	8.5	3.6	No difference in mortality
		n (AIS head ≥ *3)*	59	28	*LOS, d*	27.0	39.9§	
Bone et al. (1994)[32]†	No, included femur, pelvis, acetabulum, bilateral tibia, or tibia and additional fracture		≤48 h	Delayed	*Mortality, %*	20.2	40.7*	Early treatment: ↓ mortality
		n (GCS 3–8)	168	216				
		Note: Delayed group composed of patients from ACS Multiple Trauma Outcome Study database, who were assumed to undergo delayed treatment (actual time of treatment unknown)						
Jaicks et al. (1997)[40]	No, included upper and lower extremity fracture (15 femur fractures)		≤24 h	>24 h	*Intraoperative crystalloid, L*	4.7	2.2*	Delayed treatment: ↓ intraoperative fluid administration; no difference in mortality or LOS
		n	19	14				
		GCS	11.6	10.8	*Intraoperative SBP < 90 mm Hg, %*	16	7	
		AIS head	3.3	3.1				
		Average time to definitive treatment, h	6.8	84.3*	*Intraoperative O_2 saturation < 90%*	11	7	
					Discharge GCS	13.5	15.0	
					Mortality, %	11	0	
					Vent, d	6.4	6.5	
					LOS, d	22.0	27.0	
Starr et al. (1998)[41]	Yes		≤24 h	>24 h	*PE, %*	0.0	0.0	No difference in ARDS, mortality or LOS
		n (GCS ≤ *8)*	5	12	*Pneumonia, %*	20.0	75.0	
		ISS	32	34.3	*ARDS, %*	0.0	0.0	
		GCS	6.2	5.6	*Mortality, %*	0.0	8.3	
		AIS head	4.2	4.1	*Vent, d*	6.6	12.7	
		AIS chest	1.2	1.9	*LOS, d*	28.8	31.5	
		Note: 25% of delayed group did not undergo fracture surgery						

Kalb et al. (1998)[42]	No, included orthopedic injury (AIS ≥ 2) requiring operative fixation		≤24 h	>24 h	*Intraoperative crystalloid, L*	3.2	1.7*	Delayed treatment: ↓ fluid administration; no difference in mortality or LOS
		n	84	39				
		ISS	33	31	*Intraoperative SBP < 90 mm Hg, %*	8.3	20.5	
		AIS head	4.0	3.9				
					Intraoperative O2 saturation < 90%	15.5%	33.3%	
					Intraoperative ICP > 20 mm Hg, %	21	33	
					Discharge GCS	13.6	14	
					Mortality, %	10	8	
					ICU, d	11	10	
					LOS, d	20	19	
Velmahos et al. (1998)[43]	No, included long bone fracture (10 femur fractures)		≤24 h	>24 h	*Intraoperative fluids, mL*	2,426	1,754	No difference in mortality or LOS
		n	22	25				
		ISS	25	23	*Intraoperative SBP < 90 mm Hg, %*	41	24	
		GCS	5.8	5.7				
		AIS head	3.8	3.4	*Intraoperative O_2 saturation < 94%*	14%	4%	
		Average time to definitive treatment, *h*	17	143*				
					Discharge GCS	12	12	
					Mortality, %	5	8	
					Vent, d	8	9	
					LOS, d	17	25	
Scalea et al. (1999)[44]	No, included pelvic and lower extremity fracture		≤24 h	>24 h	*Intraoperative crystalloid, median, mL*	8,070	6,483*	No difference in mortality or LOS
		n	147	24				
		ISS	38.0	37.6				
		GCS	9.0	10.0	*Discharge GCS*	14	14.5	
		AIS head ≥ 3	76%	92%				
					Mortality, %	10	17	
					Vent, median, d	12	11	
					LOS, median, d	23	22	
Brundage et al. (2002)[34]†‡	Yes		≤24 h	>24 h	*Discharge GCS*	14.4	13.5,[a] 14.0,[b] and 12.1[c]	Early treatment: ↓ ARDS; no difference in mortality or LOS
		n (AIS ≥ 2)	283	65,[a] 17,[b] and 13[c]				
		ISS	NR	NR	*Pneumonia, %*	14	25,[a] 24[b]* and 7.7[c]	
		AIS head	3.80	3.05[a], 3.11[b], 2.94[c]				
		AIS chest	1.12	1.48[a], 1.53[b], 1.54[c]	*ARDS, %*	7.4	12,[a] 29,[b]* and 7.7[c]	
					Mortality, %	3.9	4.6,[a] 0.0,[b] and 7.7[c]	
					ICU, d	4.01	6.47,[a] 12.9,[b] and 7.89[c]§	
					LOS, d	15.5	18.8,[a] 24.3,[b] and 23.8[c]§	

[a]>24–48 h; [b]>48–120 h; [c]>120 h

Note: *p* values are calculated relative to the early group

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TABLE 5. *(Continued)*

Reference	Only Femoral Shaft Fractures Included?	Time Points			Outcomes			Conclusion
			Early	Delayed		Early	Delayed	
Wang et al. (2007)[45]	No, included orthopedic or facial fracture (16 patients with femur fracture)		≤24 h	>24 h	*Intraoperative SBP < 90 mm Hg, %*	26	19	No difference in ARDS, mortality, or LOS
		n	27	34				
		ISS, median	29	29	*Intraoperative ICP > 20 mm Hg, %*	44	25	
		GCS, median	9	7				
		AIS head, median	5	5	*Intraoperative Pao$_2$ < 60 mm Hg, %*	2	6	
		AIS chest	0.6	1.1	*FES, %*	2	0	
					PE, %	2	2	
					Pneumonia, %	23	42	
					ARDS, %	5	2	
					Sepsis, %	0	0	
					Mortality, %	4.7	3.8	
					LOS, median, d	13	17	
Nahm et al. (2011)[24]†‡	No, included intertrochanteric and femoral neck fractures		≤24 h	>24 h	*PE, %*	0.0	0.0	No difference in ARDS or mortality
		n (GCS ≤ 8)	44	22	*Pneumonia, %*	22.7	27.3	
		ISS	35.9	45.3*	*ARDS, %*	4.5	9.1	
					Sepsis, %	4.5	22.7*	
					MOF, %	0.0	4.5	
					Mortality, %	4.5	9.1	

*$p < 0.05$.
†Reference also included in Table 1.
‡Reference also included in Table 7.
§p value could not be determined.
↓, decreases; ↑, increases; ACS, American College of Surgeons; GOS, Glasgow Outcome Scale; ICU, intensive care unit length of stay; ISS, Injury Severity Score; NR, not reported; SBP, systolic blood pressure; Vent, length of time on mechanical ventilation.

TABLE 6. Head Injury (13 Studies)

	References Reporting	Early Definitive Treatment	Delayed Definitive Treatment	No Difference
ARDS	38.5% (5/13)	20.0% (1/5)[34]	0.0% (0/5)	80.0% (4/5)
Mortality rate	100.0% (13/13)	15.4% (2/13)[34,38]	0.0% (0/13)	84.6% (11/13)
LOS	46.2% (6/13)*	0.0% (0/6)	0.0% (0/6)	100.0% (6/6)

*p values could not be determined for two references,[31,34] which are not included.

reported an average of 14.0 hours between hospital admission and surgery in their early group, a time difference that may allow adequate resuscitation.[53]

Other studies focused on in-hospital mortality as a primary outcome. Most of the studies reporting mortality rate were not able to detect a difference in mortality between early and delayed or DCO groups (Tables 2, 4, 6, and 8). However, two studies were large enough to demonstrate reduced risk for mortality associated with surgery performed 8 to 24 hours after arrival (n = 1,958)[36] or 12 to 24 hours after injury (n = 3,069).[35] Both studies concluded that adequate resuscitation in the hours before surgery is essential.

Six studies demonstrated shorter stay associated with early treatment compared with delayed treatment in heterogeneous injuries (Table 2). The largest of these studies showed a mean LOS of 10.6 days (<24 hours) versus 18.5 days (>24 hours) ($p < 0.001$).[24] No studies showed a difference in LOS between early and delayed treatment in head injury. The presence of severe injuries, including head injuries, may have a stronger effect on the LOS than the timing of fracture surgery.

Head Injury

Morbidity associated with intraoperative hypotension and/or hypoxia during early fracture surgery remains a primary concern for patients with head injury. A small study (n = 33) demonstrated higher intraoperative fluid requirement for patients with severe head injury treated early as compared with those with delayed treatment (Table 7).[40] However, no difference in incidence of intraoperative hypotension/hypoxia or discharge Glasgow Coma Scale (GCS) score was detected, making the clinical significance of this finding uncertain. Three additional studies also reported no difference in incidence of intraoperative hypotension/hypoxia between early and delayed treatment.[42,43,45] Finally, six studies demonstrated no difference in long-term neurologic outcomes, measured by discharge GCS or LOS.[34,40,42–45] These findings suggest that with appropriate intraoperative intracranial pressure (ICP) monitoring and modern critical care assessment and treatment, neurologic outcomes are independent of surgery timing.

Chest Injury

In support of the role of chest injury in the two-hit hypothesis, Pape et al.[47] reported an increased incidence of ARDS

TABLE 7. References Comparing Early and Delayed Treatment in Patients with Chest Injury

Reference	Only Femoral Shaft Fractures Included?	Time Points			Outcomes			Conclusion
			Early	Delayed		Early	Delayed	
Pelias et al. (1992)[46]	No, included femur, isolated tibia, tibia/fibula, and humerus fracture (39 femur fractures)		≤48 h	>48 h	*Pulmonary complications*	27.6%	29.4%	No difference in mortality
		n	65	17				
		ISS	25.2	26.6*	*Mortality, %*	16.9	17.6	
					Vent, d	5.3	5.4	
	Note: Delayed group also included nonoperative cases (number not specified). Pulmonary complications included recurrent pleural effusions, pneumonia, empyema, ARDS, FES, and PE							
Pape et al. (1993)[47]	Yes		≤24 h	>24 h	*PE, %*	0.0	0.0	Delayed treatment: ↓ ARDS; no difference in mortality
		n (AIS chest ≥ 2)	24	26	*ARDS, %*	33.0	7.7†	
		ISS, median	33.4	32.4	*Sepsis, %*	12.5	19.2	
		GCS, median	12.1	13.7	*MOF, %*	8.3	0.0	
		AIS head	1.8	2.1	*Mortality, %*	21.0	4.0	
		AIS chest	3.3	3.4				
Fakhry et al. (1994)[31]‡	Yes		≤1 d	>1 d	*Mortality, %*	4.3	0.0	No difference in mortality

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TABLE 7. *(Continued)*

Reference	Only Femoral Shaft Fractures Included?	Time Points			Outcomes			Conclusion
			Early	Delayed		Early	Delayed	
Charash et al. (1994)[48]	Yes		≤24 h	>24 h	*PE, %*	4	4	Early treatment: ↓ pneumonia; no difference in ARDS, mortality, or LOS
		n (AIS chest ≥ 2)	57	25	*FES, %*	0.0	4	
		ISS	27	29	*Pneumonia, %*	14	48†	
		GCS	13	12	*ARDS, %*	4	8	
		AIS chest	3.3	3.4	*Mortality, %*	4	8	
					Vent, d	6.3	10	
					LOS, d	20	25	
Boulanger et al. (1997)[49]	Yes		≤24 h	>24 h	*ARDS, %*	4	20	No difference in ARDS
		n (AIS chest ≥ 2)	68	15				
		ISS	30	39*				
		AIS chest	3.3	3.7*				
Brundage et al. (2002)[34]‡	Yes		≤24 h	>24 h	*Pneumonia*	20	28,[a] 43,[b] and 12[c]	Early treatment: ↓ ARDS and LOS; no difference in mortality
		n (AIS chest ≥ 2)	186	43,[a] 14,[b] and 8[c]				
		ISS	27.11	28.95,[a] 29.71,[b] and 30.63[c]	*ARDS, %*	12	19,[a] 64,[b]† and 0.0[c]	
		AIS head	1.70	2.21,[a] 1.64,[b] and 2.63[c]*				
		AIS chest	3.02	3.14,[a] 3.21,[b] and 3.13[c]	*Mortality, %*	4.8	4.6,[a] 0.0,[b] and 12[c]	
					ICU, d	4.51	9.59,[a] 27.4,[b]† and 8.17[c]	
					LOS, d	17.7	21.4,[a] 42.0,[b]† and 23.1[c]	
		[a]>24–48 h; [b]>48–120 h; [c]>120 h						
		Note: *p* values are calculated relative to the early group						
Nahm et al. (2011)[24]‡	No, included intertrochanteric and femoral neck fracture		≤24 h	>24 h	*PE, %*	3.3	0.0	Early treatment: ↓ sepsis; no difference in ARDS or mortality
		n (AIS chest ≥ 3)	122	49	*Pneumonia, %*	22.1	28.6	
		ISS	34.4	41.4	*ARDS, %*	5.7	8.2	
					Sepsis, %	2.5	10.2†	
					MOF, %	4.1	8.2	
					Mortality, %	3.3	4.1	

*p value could not be determined.
†$p < 0.05$.
‡Reference also included in Tables 1 and 5.
↓, decreases; ↑, increases; FES, fat embolism syndrome; ICU, intensive care unit length of stay; ISS, Injury Severity Score; NR, not reported; PE, pulmonary embolism; Vent, length of time on mechanical ventilation.

TABLE 8. Chest Injury (Seven Studies)

	References Reporting	Early Definitive Treatment	Delayed Definitive Treatment	No Difference
ARDS	71.4% (5/7)	20.0% (1/5)[34]	20.0% (1/5)[47]	60.0% (3/5)
Mortality rate	85.7% (6/7)	0.0% (0/6)	0.0% (0/6)	100.0% (6/6)
LOS	28.6% (2/7)	50.0% (1/2)[34]	0.0% (0/2)	50.0% (1/2)

*p values could not be determined for one reference,[31] which is not included.

(33% vs. 8%, $p < 0.05$) for patients with chest injury (AIS score ≥ 2) who underwent early operative orthopedic treatment ($\leq$24 hours) compared with those who underwent delayed treatment. In a study using similar methodology, Charash et al.[48] detected no difference in the rate of ARDS in the early (4%) versus delayed (8%) group (both with chest AIS score ≥ 2), concluding early fracture fixation to be a sound practice. This conclusion has been supported by the findings of other North American studies investigating the effect of femur fracture fixation for patients with chest injury.[59–61] The different recommendations of these studies may benefit from further investigation.

Limitations

The results of studies were not combined to produce summary measures owing to biases inherent in this process as applied to this body of literature. Advances in critical care make comparisons of mortality and ARDS from recent studies with those published in previous decades difficult. Furthermore, many studies included patients with fractures at other anatomic sites, including the tibia, pelvis, and other long bones. The presence of these injuries may bias the results of this type of analysis. Finally, differences in definition of early treatment, multiple injuries, and ARDS may also confound results. This review was also limited by the exclusion of German-language reports, which contributed significantly to this area. In addition, although a broad-search strategy was used, relevant reports may not have been included.

Future Study

Although indications for DCO have been suggested in the literature,[6,17,18,20,33,50,56,57,62] these parameters require further validation.[20,63] Severe abdominal injury may prove to be an indication for DCO because it has been shown to be a very strong risk factor for mortality,[35] ARDS,[64] and other pulmonary complications caused by massive associated hemorrhage.[24] In this context, further prospective evaluation is also ongoing at North American trauma centers to evaluate a protocol for definitive fixation based on adequacy of resuscitation. Finally, applying DCO concepts to injuries located at other anatomic locations, for example at the proximal femur, acetabulum or thoracolumbar spine, could be an area of further investigation.[65]

AUTHORSHIP

H.A.V. designed this study. N.J.N. and H.A.V. performed the literature search. N.J.N. collected the data. N.J.N. and H.A.V. analyzed the data, which N.J.N. and H.A.V. interpreted. N.J.N. drafted the manuscript, which H.A.V. edited and critically revised.

DISCLOSURE

The authors declare no conflicts of interest.

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