SYSTEMATIC REVIEW

Factors Associated with Development of Traumatic Acute Compartment Syndrome: A Systematic Review and Meta-analysis

Sharri J. Mortensen, MD[1*]; Sebastian Orman, MD[2*]; Joseph Serino, MD[3*]; Amin Mohamadi, MD, MPH[1]; Ara Nazarian, PhD[1,5,6**]; Arvind von Keudell, MD[4,5**]

Research performed at Brigham and Women's Hospital, Boston, MA, USA

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Abstract

Background: Acute compartment syndrome (ACS) is a devastating condition, further aggravated by delayed diagnosis. Since ACS is a clinical diagnosis, identification of risk factors for individual patients may help with earlier detection. This study aims to identify the risk factors associated with the development of ACS of the extremities.

Methods: We performed a systematic review and meta-analysis of studies with adult patients at risk for and with traumatic ACS of the extremity. Non-traumatic, chronic exertional, vascular and abdominal compartment syndrome were excluded. Technical reports, biomechanical studies, abstracts, studies of non-human subjects, non-English studies, and studies with less than five subjects were excluded. Meta-analysis was performed on a subset of studies including a control group. We addressed cases of substantial heterogeneity among the studies with subgroup analysis, and whenever heterogeneity remained significant, we employed random effect meta-analysis for the data pooling. The study protocol has been registered in PROSPERO (ID = CRD42019126603).

Results: There were 19 studies with 48,887 patients investigating risk factors of traumatic ACS. Of these, there were 1,716 patients with the diagnosis of traumatic ACS. Fourteen studies (46,300 controls and 1,358 ACS patients) qualified for meta-analysis. Male to female ratio was 5.5 with an average age of 36 years. Factors that were significantly associated with the development of ACS were: age 18-64 (OR: 1.34, 95% CI: 1.07-1.68), male (OR: 2.18, 95% CI: 1.53-3.10), gunshot wound with fracture and vascular injury (OR: 12.5, 95% CI: 5.69-27.46), combined forefoot and midfoot injury (OR: 3.3, 95% CI: 2.39-4.57), injury severity score (ISS) 0-9 (OR: 1.58, 95% CI: 1.27-1.97), OTA/AO type C fractures (OR: 2.75, 95% CI: 1.04-7.28), vascular injury (OR: 9.05, 95% CI: 6.69-12.26), and high-energy trauma (OR: 3.10, 95% CI: 1.60-5.82). Factors such as tibia fracture and crush injury were reported but were not included in quantitative analysis, due to lack of control groups and/or only one study qualifying for meta-analysis.

Conclusion: This study reports on the current significant risk factors for developing traumatic ACS. The most common risk factors included age, sex, gunshot wound with a vascular injury, OTA/AO fracture type C and high-energy trauma.

Level of evidence: II

Keywords: Acute disease, Adult, Compartment syndromes/diagnosis, Compartment syndromes/surgery, Humans, Risk assessment

Introduction

Acute compartment syndrome (ACS) is a condition caused by increased pressure in a confined anatomic space, resulting in decreased perfusion, hypoxia, and potential necrosis of the involved tissues over time (1). While fracture of the tibial shaft appears to have the strongest association with ACS, other anatomic

Corresponding Author: Sharri J. Mortensen, Center for Advanced Orthopaedic Studies, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
Email: smortens@bidmc.harvard.edu

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regions are also at risk, including the forearms and thighs (2). Etiologies are extensive and include fracture, arterial injury, reperfusion injury, crush injury, burns, electrocution, snake venom, IV infiltration, prolonged malposition, and medical conditions such as nephrotic syndrome, rhabdomyolysis, bleeding disorders, and post-resuscitation systemic inflammatory response syndrome (1, 3).

The diagnosis of ACS involves serial clinical exams with recognition of the three "P's" – pain (out of proportion of exam, especially with passive stretch), paresthesia and paralysis (2). The likelihood of ACS and the risk of irreversible disability increases when multiple of these clinical signs are present. Late findings such as paresthesia and paralysis are usually irreversible (4, 5). Therefore, while acute compartment syndrome has traditionally been diagnosed clinically, clinical symptoms often occur too late for optimal intervention and prevention of long term sequalae (1). A common adjunct for diagnosing acute compartment syndrome involves serial exams with manual palpation of compartment firmness. However, physician ability to detect elevated compartment pressures is poor, with a documented sensitivity and specificity of 24% and 55%, respectively (6). Invasive compartment pressure monitoring has become an important adjunct to diagnosis to help determine the need for fasciotomy. Current evidence suggests a perfusion pressure (ΔP) of ≤ 30 mmHg, in addition to clinical findings, is the most accurate means of diagnosis (1, 7). Several non-invasive diagnostic modalities are also currently under investigation (8).

Definitive and early treatment of ACS (within 4 hours) is of critical importance and involves decompression of the involved compartments with fasciotomy (3, 9). In one study, fasciotomy within 12 hours of ACS onset resulted in return of normal function in 68% of extremities with a complication rate of 4.5%, compared to a success rate of 8% and complication rate of 54% with delayed treatment (10). Missed diagnosis or delayed treatment may result in significant and irreversible complications, including neuropathy, muscle necrosis, contractures, infection, and even death. However, unnecessary fasciotomy is also associated with unfavorable outcomes (11). Therefore, both accurate and timely diagnosis is essential for satisfactory patient outcomes. Since diagnosis of ACS is clinical, considering risk factors for ACS can help clinicians to identify patients at higher risk and more accurate diagnosis. There are several studies reporting on risk factors associated with the development of ACS, however there are inconsistencies among these reports.

Objectives

The purpose of this study was to identify the most reliable risk factors associated with the development of extremity ACS in order to facilitate early and accurate diagnosis. We do so by reporting on the pooled odds ratio of these risk factors.

Materials and Methods

In February of 2019, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) Group guidelines, we electronically searched the MEDLINE, EMBASE, Web of Science, and Google Scholar databases. The protocol for this systematic review and meta-analysis has been registered at PROSPERO (ID = CRD42019126603). After removal of duplicates, 4,048 studies were identified. First round of screening based on title and abstract yielded 164 articles. There were 19 articles included after reviewing the full texts for eligibility [Figure 1].

The following search strategy was developed for MedLine and was then adapted for the other databases: ("Compartment Syndromes"[mesh] OR compartment syndrome*[tiab]) AND ("Arm"[mesh] OR "Leg"[mesh] OR arm[tiab] OR forearm*[tiab] OR hand[tiab] OR hands[tiab] OR finger*[tiab] OR thumb[tiab] OR leg[tiab] OR calf[tiab] OR calves[tiab] OR thigh*[tiab] OR foot[tiab] OR feet[tiab] OR toe[tiab] OR toes[tiab] OR heel[tiab] OR extremit*[tiab] OR limb*[tiab]) AND ("Risk"[mesh] OR "Predictive Value of Tests"[Mesh] OR "Odds Ratio"[mesh] OR "Proportional Hazards Models"[mesh] OR risk[tiab] OR predict*[tiab] OR associated[tiab] OR association[tiab] OR odds ratio[tiab] OR hazard ratio[tiab] OR proportional hazard*[tiab] OR cox[tiab] OR logistic[tiab]).

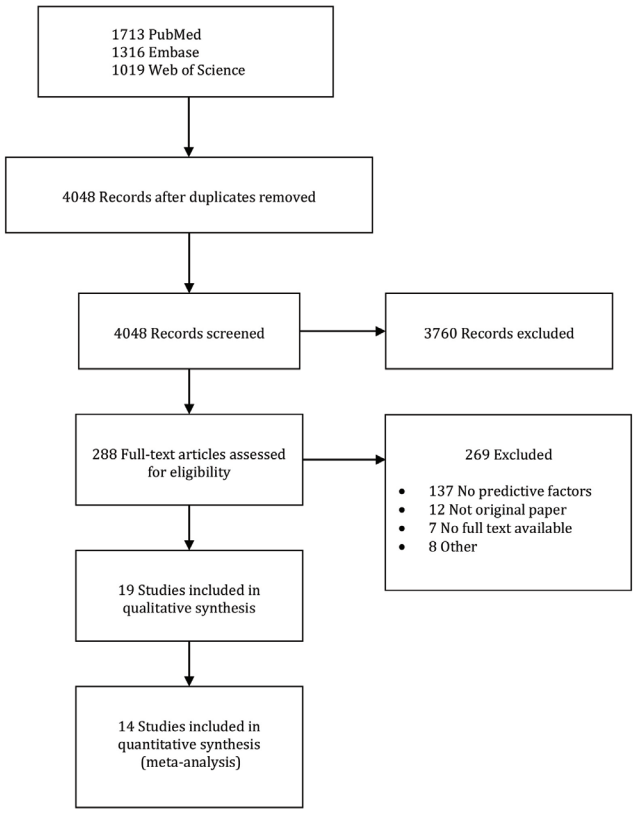


Figure 1. PRISMA flow diagram.

Study Selection

Retrospective and prospective studies of patients at least 18 years of age with acute, traumatic extremity compartment syndrome were considered eligible for our study. An initial screening of the search results was performed based on title and abstract to exclude studies that did not meet eligibility criteria. This was followed by a full-text review of the remaining studies. Studies involving atraumatic compartment syndrome, chronic exertional compartment syndrome, vascular ACS, abdominal ACS, and ACS secondary to burns were excluded. Technical reports, biomechanical studies, abstracts, studies of non-human subjects, non-English studies, and studies with less than five participants were also excluded. Study selection was performed by two independent reviewers. Disagreements were solved by an attempt to reach a consensus, and if necessary, a third reviewer resolved the disagreement [Figure 1. Flowchart of systematic review].

Data Extraction and Critical Appraisal

Our data extraction sheet was based on the Cochrane Consumers and Communication Review Group's data extraction template. Data extraction was performed by a single investigator then reviewed for accuracy and consistency by a second investigator. The following information was extracted from each study: first author, year published, country published, mean age, sex ratio, recruitment period, follow-up time, number of patients, number of controls, mechanism of injury, type of injury, ACS risk factors identified, and any confounding variables that were adjusted for during analysis as well as level of evidence reported by original studies. Level of evidence for each study was noted based on the Oxford Centre for Evidence-based Medicine levels of Evidence. Two reviewers independently assessed the methodological quality of all included studies using the Newcastle-Ottawa Quality Assessment Scale (NOS). This tool is used to assess the risk of bias in non-randomized studies by rating each study based on selection of study groups, comparability of these groups, and outcomes. It employs a "star-system" with a maximum rating of 9 stars.

Statistical Analysis

Statistical analysis was performed with Comprehensive Meta-Analysis Version 2.2064 (Biostat, Englewood, NJ, USA). We synthesized effect sizes for risk factors using the number of exposed and unexposed subjects in case and control group (i.e. crude data), and odds ratios or relative risk whenever the factor was reported by at least two studies. Relative risk and risk ratios were converted to OR given the uncommon nature of ACS. Adjusted odds ratios (i.e. OR from multivariable analysis) were favored if available in the studies. Cochran's Q statistic was calculated to assess heterogeneity among individual included studies, with a p-value < 0.10 used for statistical significance due to concerns for low sensitivity. The I^2 statistic was used to demonstrate low (0%–25%), moderate (26%–50%), substantial (51%–75%), or considerable (> 75%) inconsistency (12). Cases of substantial or higher heterogeneity among the studies (p-value < 0.1 and/or I2 > 50%) were addressed by subgroup analysis, and whenever heterogeneity remained significant, we employed random effect meta-analysis for the data pooling. When enough data was reported for different site of ACS, we ran sensitivity analyses based on the site in order to assess whether the site of ACS could be the source of heterogeneity. In cases where the site of ACS was found to have contributed to the heterogeneity, we reported the outcomes (i.e. pooled OR) for each site separately. The sensitivity analyses are reported in appendix [Appendix].To assess publication bias, we used the Begg-Mazumdar test with a *P-value* of 0.05 as well as visual inspection of a funnel plot.

We also assessed the strength of supporting evidence for each risk factor, from grade I to III, on the basis of the combination of heterogeneity and total number of enrolled patients (grade of evidence).

Source of funding

No funding was received for this study and none of the authors have a conflict of interest.

Results

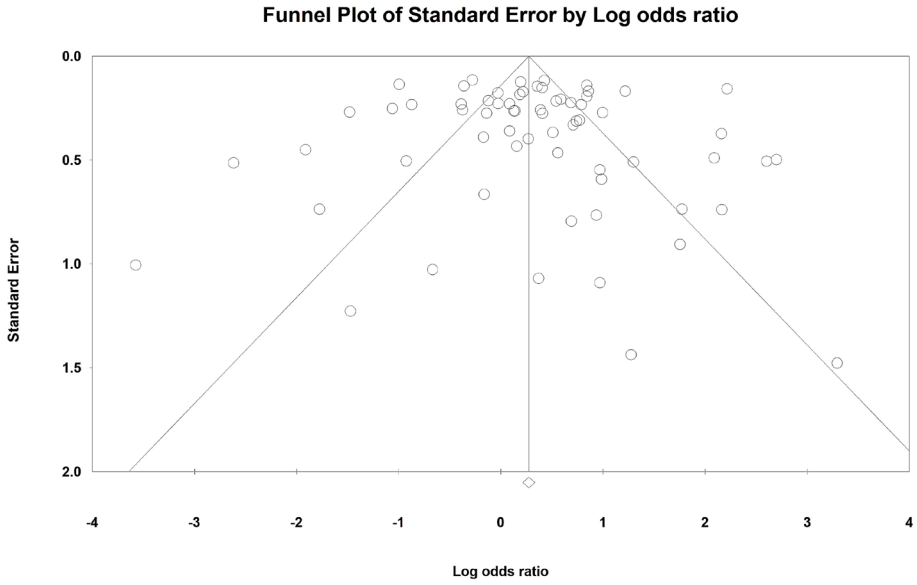
There were 19 studies with 48,887 patients investigating risk factors for traumatic ACS dating from 1991 to 2018[13-31]. Of these, there were 1,716 patients with the diagnosis of traumatic ACS. Fourteen studies with 47,658 patients were included in the meta-analysis, of which 1,358 had traumatic ACS. The sample size of the studies ranged from 131 to 18,676 patients. The overall male to female ratio was 5.5 with an average age of 36 years. All of the studies included in the meta-analysis were retrospective and were ranked 7 or higher on the Newcastle-Ottawa Scale [Table 1]. No significant publication bias was noted in this review, with the Begg and Mazumdar's test for rank correlation resulting a *P-value* of 0.68 [Figure 2. Funnel plot].

Factors that were significantly associated with the development of ACS were: age 18-64 (pooled OR: 1.34, 95% CI: 1.07-1.68), male (pooled OR: 2.18, 95% CI: 1.53-3.10), gunshot wound with fracture and vascular injury (pooled OR: 12.5, 95% CI: 5.69-27.46), combined forefoot and midfoot injury (pooled OR: 3.3, 95% CI: 2.39-4.57), injury severity score (ISS) 0-9 compared to ISS >9 (pooled OR: 1.58, 95% CI: 1.27-1.97), OTA/AO type C fractures (pooled OR: 2.75, 95% CI: 1.04-7.28), vascular injury (pooled OR: 9.05, 95% CI: 6.69-12.26), and high-energy trauma (pooled OR: 3.10, 95% CI: 1.60-5.82). Factors with a decreased risk of ACS included age 65 years (pooled OR: 0.13, 95% CI: 0.04-0.39), low energy trauma (pooled OR: 0.35, 95% CI 0.19-0.63) and isolated forefoot injury (pooled OR: 0.76, 95% CI: 0.62-0.95) [Table 2; Figure 3]. The sensitivity analyses based on the site of ACS found the gender male and open fracture to be contributing factors to the heterogeneity for these risk factors, thus they are also reported separately in table 2. The other risk factors were not found to have contributed to the heterogeneity nor the odds ratio (Appendix).

Table 1. Characteristics of studies included in the systematic review

Study	Year	Country	Recruitment period	Average Age (years)	Sex (M:F)	Site of ACS	No. Patients with ACS	No. Patients without ACS	NOS	Level of Evidence
Beebe et al (13)	2017	USA	2006-2016	43	2	Leg	136	2,749	9	III
*Berg et al (14)	2012	USA	2002-2008	27	9	All	53	6,934	9	III
Branco et al (15)	2011	USA	1998-2007	36	3	All	288	10,027	9	III
Gamulin et al (16)	2017	Switzerland	2005-2009	49	1	Leg	28	241	9	III
Gonzalez et al (17)	2009	USA	1998-2006	31	13	Leg	31	290	7	III
*Guerrero et al (18)	2002	USA	1985-1999	29	5	Leg	17	134	7	III
*Haller et al (19)	2016	USA	2006-2012	43	2	Leg	14	145	8	III
Kim et al (20)	2009	USA	1985-2001	28	9	UE	29	110	8	III
*Lollo et al (21)	2016	USA	2007-2011	NR	5	Leg	124	0	5	III
*McQueen et al (22)	2000	UK	1995-2007	39	2	Leg	164	0	5	III
McQueen et al (23)	2015	UK	1995-2007	39	2	Leg	160	1,228	9	III
Meskey et al (24)	2011	USA	2001-2007	28	14	All	23	627	7	III
Moed et al (25)	1991	USA	1980-1988	28	13	UE	13	118	8	III
Park et al (26)	2018	South Korea	2008-2016	47	2	Feet	29	760	7	III
Shagdan et al (27)	2015	Canada	1997-2011	41	2	Leg	87	1,038	9	III
Thakur et al (28)	2012	USA	2002-2008	38	2	Feet	364	18,312	8	III
Valdez et al (29)	2013	USA	2001-2011	45	NR	Leg	39	592	7	III
Wind et al (30)	2012	USA	2006-2009	20	4	Leg	34	592	7	III
Zuchelli et al (31)	2017	USA	2010-2014	44	1	All	83	3,274	9	III

ACS= Acute compartment syndrome, NOS=Newcastle Ottawa Scale, UE=Upper extremity,
* These studies were not included in the meta-analysis



No significant asymmetry present, Begg and Mazumdar's test for rank correlation yields a *P-value* of 0.68

Figure 2. Funnel plot.

Table 2. Pooled Odds Ratios of risk factors for traumatic acute compartment syndrome

Factors	No. of Studies	Patients without ACS, N	Patients with ACS, N	Pooled OR (95% CI)	*P-value*	Heterogeneity: I2 (P-value)	Grade of Evidence
Demographics							
Age 18-64	2(23, 28)	19,540	524	1.34 (1.07-1.68)	0.01	0 (0.47)	I
Age >65 yr *	4(15, 23, 28, 31)	32841	895	0.13 (0.04-0.39)	0.01	82 (0.001)	II-A
Male *!	9(13, 15, 16, 23, 24, 26-28, 31)	38,256	1,198	2.18 (1.53-3.10)	<0.001	76.9 (<0.001)	II-A
Male, mixed ACS site*	3(15, 24, 31]			4.13 (1.3-13.08)	0.02	79 (0.01)	
Male, leg ACS	4(13, 16, 23, 27)			1.40 (1.15-1.69)	0.001	48 (0.12)	
Male, feet ACS	2(26, 28)			2.27 (1.74-2.95)	<0.001	0 (0.56)	
Comorbidity	2(26, 31)	4,034	112	1.31 (0.86-1.99)	0.213	0 (0.41)	II-B
Smoking	2(23, 26)	1,988	189	1.10 (0.71-1.54)	0.813	0 (0.52)	III
Type of Injury							
GSW with fracture and vascular injury	3(14, 17, 25)	7,342	97	12.50 (5.69-27.46)	<0.001	0 (0.77)	I
Forefoot injury	2(26, 28)	19,072	393	0.76 (0.62-0.95)	0.015	0 (0.79)	I
Fore- and midfoot injury	2(26, 28)	19,072	393	3.31 (2.39-4.57)	<0.001	0 (0.52)	I
Fore-, mid- and hindfoot injury	2(26, 28)	19,072	393	2.14 (1.19-3.85)	0.012	0 (0.84)	I
Hindfoot injury *	2(26, 28)	19,072	393	0.61 (0.20-1.87)	0.388	84 (0.01)	II-A
Midfoot injury	2(26, 28)	19,072	393	0.87 (0.53-1.43)	0.577	0 (0.97)	I
Mid-and hindfoot injury	2(26, 28)	19,072	393	0.50 (0.21-1.23)	0.132	17 (0.27)	I
Open fracture*!	6(13, 15, 16, 20, 23, 27)	15,152	628	1.24 (0.74-2.10)	0.415	69 (0.01)	I
Open fracture, leg	4(13, 16, 23, 27)			0.86 (0.64-1.18)	0.35	51 (0.11)	
Injury Severity Score 0-9	2(27, 28)	19,350	451	1.58 (1.27-1.97)	<0.001	0 (0.42)	I
Injury Severity Score >16 *	2(15, 28)	28,339	652	1.02 (0.48-2.16)	0.956	92.5 (<0.001)	II-A
OTA/AO Fracture type B	2(13, 23)	3,977	296	1.30 (0.89-1.89)	0.17	0 (0.47)	II-B
OTA/AO Fracture type C *	3(13, 16, 23)	4,218	324	2.75 (1.04-7.28)	0.042	82 (0.004)	III
Vascular injury	2(15, 20)	10,137	317	9.05 (6.69-12.26)	<0.001	0 (0.62)	I
Mode of Injury							
* High energy trauma	6(16, 23, 26, 27, 30, 31)	7,133	421	3.0 (1.60-5.82)	0.001	82 (<0.001)	II-A
* Low energy trauma	4(23, 26, 27, 31)	6,300	359	0.35 (0.19-0.63)	<0.001	73.4 (0.01)	II-A

* Random effect model was used for these variables due to significant heterogeneity
! Site of ACS was found to be a source of heterogeneity, thus the risk factor reported separately for the sites of ACS

Discussion

Main Findings

There is a relatively small body of knowledge on predictive factors for ACS. This is the first meta-analysis reporting on risk factors associated with the development of ACS following a traumatic injury. We found several significant risk factors, including the age range of 18-64 years, male sex, gunshot wound with fracture and vascular injury, combined forefoot and midfoot injury, injury severity score (ISS) 0-9, OTA/AO type C fractures, vascular injury, and high-energy trauma. Factors such as tibia fracture and crush injury were reported but were not analyzable, due to lack of control groups and/or only one study qualifying for meta-analysis. Crush injuries

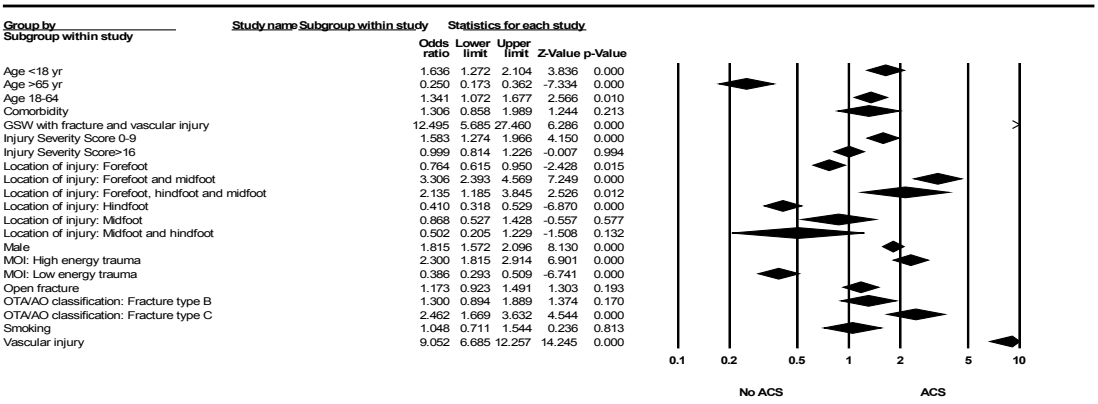


Figure 3. Forest plot.

were likely included in the reports of high-energy trauma, which was found to be significantly associated with ACS.

ACS occurs most commonly after a traumatic insult; however, the condition can also develop following a period of ischemia, reperfusion, burns, or prolonged limb compression (32-35). We chose to include risk factors for ACS following traumatic injuries only, since different etiologies and mechanisms for ACS may be associated with disparate risk factors.

Demographics as Risk Factor

It is well established in the literature that younger patients are at higher risk for developing ACS (23, 28, 36). Our study was able to perform meta-analysis on two age ranges (18-64 years, and ≥ 65 years) and showed that an age of 18-64 was a significant risk factor for the development of ACS. This is consistent with common knowledge among treating physicians. Male gender has similarly been recognized as a risk factor for developing ACS, despite the lack of significance reported by Shadgan *et al.* in a large cohort study (27). However, our results support the rest of the literature, finding male sex to be associated with increased odds of developing ACS. Men have a higher risk of being involved in motor vehicle accidents and sporting accidents, and they tend to participate in dangerous endeavors, which may increase their risk of high-energy and severe trauma (37). The fact that there are more men than women with severe traumatic injuries might explain why the majority of ACS patients in our study were male.

Type of Injury as Risk Factor

Vascular injury and gunshot wound with fracture and vascular injury yielded the highest odds ratio for developing ACS (OR of 9 and 12.5, respectively). Several studies have reported an overall incidence of ACS of 10% following a non-fatal gunshot wound (25, 38, 39). This patient group should be highly monitored for developing ACS. It has been estimated that 50% of cases with combined popliteal artery and venous injuries require fasciotomy (34, 40]). Vascular injuries should likewise heighten the treating physician's suspicion for ACS, and continuous pressure monitoring should be considered in both of these types of injury.

There has been a misconception among physicians in the past that open fractures could be considered a protective factor in developing ACS, as it relieves the high intra-compartmental pressure (ICP). This has since been disproven, and open fractures have been shown to be associated with the development of ACS in some studies (15, 16, 41). However, we did not find open fracture to be a significant risk factor for ACS.

There is a prevailing assumption among physicians that tibia fractures are a significant risk factor for developing ACS. This stems from two of the largest cohort studies on ACS, one of which only included ACS patients and no control group and another which only included patients with tibia fractures, thus not really designed to examine the causal effect of tibia fracture on developing ACS (22, 27). We were not able to perform a meta-analysis on tibia fractures due to the lack of appropriately designed studies such as case control studies.

ACS of the forearm and the leg is widely acknowledged; however, a similar pathologic process can also occur in the foot, which is considerably less recognized and remains under- and mis-diagnosed. The pain associated with ACS of the foot eventually resolves to a degree, but other complications develop, such as joint stiffness, deformities of the toe, and full thickness skin loss. The incidence is approximately 6% in patients with foot injuries, which is actually similar or even higher than the rate of ACS in the lower leg following lower extremity trauma (42-45). We found that patients with the combination of forefoot and midfoot injuries or forefoot, midfoot and hindfoot injuries have a significantly higher risk of developing ACS. Although these patients should be monitored closely, there is a need for further studies on ACS of the foot in order to correctly diagnose the condition.

We were able to perform meta-analysis for injury severity score (ISS) of 0-9 and > 16. ISS 0-9 was found to be significantly associated with ACS. However, this finding should be interpreted with caution, since data was combined from only two studies and one of the cohorts consisted of patients with foot trauma only (27, 28). It is generally assumed that patients with higher ISS are

at higher risk of developing ACS, especially hypotensive patients, since a lower ICP is needed to develop ACS with low diastolic blood pressure (46). However, this was not the finding of Shadgan *et al.*, and might be yet another common misconception, as there is a lack of scientific proof to support this theory (27). It could be argued that patients with a high ISS have a higher mortality rate and might expire prior to the onset of ACS. Similarly, these severely ill patients might be unresponsive and in a medically induced coma, consequently masking the clinical symptoms associated with developing ACS, leading to a missed diagnosis.

Limitations

Meta-analysis studies are inherently limited by the quality of the included articles. Our quality assessment with NOS found the included studies to be of high quality. Additionally, we were only able to report on the risk factors that were included in at least two studies. Furthermore, we found some heterogeneity in our analysis which was unexplained by our sensitivity analyses. We assessed the "grade of evidence" of the risk factors which combines heterogeneity with the sample size and provides a better impression of the risk factors. Additionally, we were not able to evaluate the overall interaction between the risk factors and we did not differentiate between the sites of ACS in order to report on an overall risk factor for trauma patients.

This study reports on the current significant risk factors for developing traumatic ACS in order to heighten awareness of ACS in this subset of patients and aid in their accurate and timely diagnosis. The most common risk factors included age, sex, gunshot wound with a vascular injury, OTA/AO fracture type C and high-energy trauma. Surprisingly, there was a lack of high-quality studies to verify some of the most commonly considered risk factors, such as tibia fracture and crush injury. Further studies are warranted to identify and confirm risk factors diagnosing ACS.

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Sharri J. Mortensen MD[1*]
Sebastian Orman MD[2*]
Joseph Serino MD[3*]
Amin Mohamadi MD MPH[1]
Ara Nazarian PhD[1,5,6**]
Arvind von Keudell MD[4,5**]
1 Center for Advanced Orthopaedic Studies, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
2 Department of Orthopaedic Surgery, Warren Alpert Medical School of Brown University, Providence, RI, USA
3 Department of Orthopaedic Surgery, Rush University Medical Center, Chicago, IL, USA
4 Department of Orthopaedic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
5 Harvard Orthopaedic Trauma Initiative, Harvard Medical School, Boston, MA, USA
6 Department of Orthopaedic Surgery, Yerevan State Medical University, Yerevan, Armenia
* These authors have contributed equally as first authors.
** These authors have contributed equally as senior authors.

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Appendix. Sensitivity analyses for different sites of ACS

Factors	No. of Studies	Site of ACS	Pooled OR (95% CI)	*P-value*	Heterogeneity: I2 (*P-value*)
Demographics					
Age >65 yr	2	Mixed	0.19 (0.03-1.02)	0.053	90 (0.002)
Male	3	Mixed	4.13 (1.3-13.08)	0.02	79 (0.01)
Male	4	Leg	1.40 (1.15-1.69)	0.001	48 (0.12)
Male	2	Feet	2.27 (1.74-2.95)	<0.001	0 (0.56)
Type of Injury					
Forefoot injury	2	Feet	0.76 (0.62-0.95)	0.015	0 (0.79)
Forefoot and midfoot injury	2	Feet	3.31 (2.39-4.57)	<0.001	0 (0.52)
Forefoot and midfoot and hindfoot injury	2	Feet	2.14 (1.19-3.85)	0.012	0 (0.84)
Hindfoot injury *	2	Feet	0.61 (0.20-1.87)	0.388	84 (0.01)
Midfoot injury	2	Feet	0.87 (0.53-1.43)	0.577	0 (0.97)
midfoot and hindfoot injury	2	Feet	0.50 (0.21-1.23)	0.132	17 (0.27)
Open fracture	4	Leg	0.86 (0.64-1.18)	0.35	51 (0.11)
OTA/AO Fracture type B	2	Leg	1.30 (0.89-1.89)	0.17	0 (0.47)
OTA/AO Fracture type C *	3	Leg	2.75 (1.04-7.28)	0.042	82 (0.004)
Mode of Injury					
High energy trauma	4	Leg	3.0 (1.13-7.93)	0.03	88 (<0.001)
Low energy trauma	2	Leg	0.49 (0.25-0.95)	0.03	74 (0.05)

Enough data was only available for these risk factors to run a sensitivity analysis based on the sites of ACS