

Inflammatory and Coagulative Considerations for the Management of Orthopaedic Trauma Patients With COVID-19: A Review of the Current Evidence and Our Surgical Experience

Richard N. Puzzitiello, MD, Nicholas R. Pagani, MD, Michael A. Moverman, MD, Andrew S. Moon, MD, Mariano E. Menendez, MD, and Scott P. Ryan, MD

Summary: Mounting evidence suggests that the pathogenesis of coronavirus disease 2019 (COVID-19) involves a hyperinflammatory response predisposing patients to thromboembolic disease and acute respiratory distress. In the setting of severe blunt trauma, damaged tissues induce a local and systemic inflammatory response through similar pathways to COVID-19. As such, patients with COVID-19 sustaining orthopaedic trauma injuries may have an amplified response to the traumatic insult because of their baseline hyperinflammatory and hypercoagulable states. These patients may have compromised physiological reserve to withstand the insult of surgical intervention before reaching clinical instability. In this article, we review the current evidence regarding pathogenesis of COVID-19 and its implications on the management of orthopaedic trauma patients by discussing a case and the most recent literature.

Key Words: COVID-19, coronavirus, trauma, fracture

(*J Orthop Trauma* 2020;00:1–6)

INTRODUCTION

The coronavirus disease 2019 (COVID-19) is a novel viral illness that is precipitated by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).¹ As of April 19, 2020, COVID-19 has been diagnosed in nearly 2.3 million people worldwide, has led to over 150,000 deaths, and has been deemed a pandemic by the World Health Organization.²

In its most severe form, COVID-19 is characterized by a cytokine release syndrome (CRS) that progresses to multisystem organ failure and death.^{3,4} Recent reports also demonstrate that patients are predisposed to thromboembolic disease through both the direct and indirect effects of COVID-19.^{1,5} Although some patients require early intensive care, the majority experience a more benign clinical course. A certain subset of patients, however, mount a large inflammatory response despite initially appearing well.⁶ Early monitoring of inflammatory markers is being used to help predict

which patients will eventually necessitate higher levels of care.⁷

A similar hyperinflammatory and hypercoagulable response leading to multisystem organ failure is also seen in patients after severe polytrauma.^{8–10} A less severe initial traumatic insult (“first hit”) also has the capacity to produce the same systemic response if it is followed by persistent physiologic derangements or subsequent proinflammatory interventions (“second hit”).^{8,11,12} Damage control orthopaedics is often used in polytrauma patients to minimize the second hit and prevent subsequent acute respiratory distress syndrome (ARDS).^{13–15}

Although a trauma is often thought of as the first hit in the two-hit theory, other hyperinflammatory and hypercoagulable states, such as in COVID-19, may also act as part of the first hit in patients with orthopaedic injuries. This may be especially relevant in patients who appear well but have developed a large inflammatory response.¹⁶ Indeed, recent evidence suggests alarmingly high intensive care unit (ICU) admission and mortality rates after elective surgery on asymptomatic patients in the incubation period of COVID-19.^{16,17} However, little is known about how orthopaedic trauma and subsequent fracture fixation modulates the inflammatory response in patients with COVID-19. A better understanding of this relationship can inform the development of evidence-based management strategies in these patients and limit admissions to overcrowded ICUs.

To demonstrate and further define these developing theories on the coagulative and inflammatory risks associated with the surgical treatment of trauma patients with COVID-19, we will present an unexpected outcome on such a patient at our institution. The purpose of this case presentation is to drive the subsequent discussion and literature review on the management of patients with COVID-19 presenting with orthopaedic trauma.

OUR SURGICAL EXPERIENCE

A woman in her 80s with a history of dementia and myeloproliferative disorder presented with an isolated extra-articular fracture of the left distal femur (Fig. 1) and acute nonocclusive deep vein thromboses (DVTs) of the left popliteal and gastrocnemius veins. On presentation, she was

Accepted for publication May 12, 2020.

From the Department of Orthopaedic Surgery, Tufts Medical Center, Tufts University School of Medicine, Boston, MA.

The authors report no conflict of interest.

Reprints: Scott P. Ryan, MD, Tufts Medical Center, 800 Washington St, Boston, MA 02111 (e-mail: sryan3@tuftsmedicalcenter.org).

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

DOI: 10.1097/BOT.0000000000001842

afebrile and denied any respiratory symptoms. Her preoperative peripheral capillary oxygen saturation was between 90% and 97% on room air and at times requiring 2 L of supplemental oxygen. Physical examination revealed that the patient not to be in respiratory distress with clear lung sounds. Admission chest radiograph is shown in Fig. 2, demonstrating no major consolidation or infiltrates. Laboratory evaluation showed no leukocytosis, anemia, or thrombocytosis.

Given that she was a nursing home resident with known exposure to multiple COVID-19–positive residents, she was tested for the disease and found to be positive. A multidisciplinary approach was taken for the care of this patient, including orthopaedics, internal medicine, infectious disease, anesthesia, and vascular surgery. She was deemed an asymptomatic COVID+ patient with no concern for her respiratory function.

A shared decision was made to proceed with surgical fixation to allow for improved mobility, healing, and pain control.

Within 12 hours of initial presentation, the patient underwent reamed, locked retrograde intramedullary nailing of her left distal femur fracture. Intramedullary nailing was chosen because it is the senior author's preferred treatment for distal third femur fractures and the intramedullary implant would assist in preventing medialization of the distal segment. Preoperative templating estimated an isthmus of 16–17 mm. Plan was for placement of a 13-mm diameter nail. The patient tolerated the early steps of the procedure well. During passage of the 14-mm diameter reamer and obtaining cortical chatter, the patient became acutely hypoxic and hypotensive requiring maximal FiO₂ (P/F ratio 102) and increasing vasopressor requirements. After reaming, the patient improved marginally to the point where she was amenable to intramedullary nail placement. After placement of the intramedullary nail, a heparin drip was immediately initiated for presumed intraoperative pulmonary embolism. She remained intubated at the completion of the procedure and was transferred to the ICU.

Laboratory values obtained immediately postoperatively are provided in Table 1, along with postoperative



FIGURE 1. Preoperative anteroposterior (A) and lateral (B) radiographs of the left knee demonstrating an obliquely oriented, extra-articular fracture of the distal femur.

laboratory trends. The patient's initial leukocytosis and elevated troponin, brain natriuretic peptide, fibrinogen, D dimer, ferritin, and C-reactive protein (CRP) are noted. The patient's P/F ratio at that time declined to 88 (PaO₂ 88 mm Hg, FiO₂ 100%), indicating severe respiratory failure.

Upon arrival to the ICU, a bedside echocardiogram was performed revealing the right ventricular dilation and septal flattening indicative of right heart strain. Computed tomography pulmonary angiogram demonstrated a nonocclusive right main pulmonary artery embolus with right heart strain, left upper lobe segmental pulmonary artery embolus, and mosaic, ground glass attenuation of the lung parenchyma concerning for viral pneumonia and fat embolism. Subsequent pulmonary angiography redemonstrated the right-sided lobar embolus and elevated mean pulmonary artery pressure. Right-sided percutaneous pulmonary suction thrombectomy was performed. Blood clot and fat emboli were removed with no significant residual lobar or segmental pulmonary emboli on follow-up angiogram (Fig. 3). The patient's relatively small embolic burden did not correlate with her clinical presentation of respiratory failure with right heart strain. In addition, the patient's hemodynamic response and lack of improvement after embolectomy was not characteristic of other experiences with similar volumes of thrombus or fat extraction.

The patient required inotropic support for the first 48 hours postoperatively. She was successfully extubated on postoperative day 9 and transferred out of intensive care on postoperative day 13.

ORTHOPAEDIC TRAUMA AND COVID-19

Although the orthopaedic surgeons' role in mitigating the COVID-19 crisis may appear disparate compared with our medical colleagues, the management of patients with COVID-19 undergoing nonelective orthopaedic trauma



FIGURE 2. Preoperative anteroposterior chest radiograph demonstrating enlarged cardiomeastinal contours, low lung volumes, and bibasilar linear densities reflecting subsegmental atelectasis. No focal consolidation noted.

TABLE 1. Postoperative Laboratory Values

Hours Postoperatively	WBC	Hct	Troponin	BNP	Fibrinogen	D Dimer	Lactate	CRP
1	16.4*	37.6	0.07*	156*	488*	14,783*	1.1	57*
9	20.9*	35.4	1.08*	291*			1.9	189.5*
13	18.2*	33					1.3	
20	19.6*	31.1						
26	16.8*	32.1						
36	11.8*	27.2						
50	10.2	23†	0.26*	539*	700*			314.4*
59	11.4*	25.4						279.62*

*Indicates values above the defined reference range.

†Indicates blood transfusion.

Values in bold indicate peak.

Hct, hematocrit; WBC, white blood cell.

surgery demands thoughtful consideration. Emerging evidence in the medical literature suggests that a cytokine storm, also known as CRS, plays an integral role in severe COVID-19. Severe blunt trauma and the resulting surgical intervention similarly initiate a sequence of inflammatory events resulting in clinical instability.¹⁸ In the case we have presented, an asymptomatic COVID-19 patient with a femur fracture urgently treated with intramedullary fixation, as is the standard of care for the treatment of femoral shaft fractures. Intraoperatively, she developed pulmonary and fat emboli resulting in a systemic hyperinflammatory response and acute cardiopulmonary collapse. Our hypothesis is that the patient’s diagnosis of COVID-19 amplified the initial inflammatory response to the low-energy traumatic insult (“first hit”) that was not clinically apparent preoperatively. In addition, the hypercoagulable state secondary to COVID-19 and the inflammatory load of intramedullary reaming, fat emboli, and pulmonary embolism resulted in a “second hit” that may have cumulatively pushed our patient past a “tipping point” and into respiratory failure (Fig. 4). We would not have expected this type of response during intramedullary fixation of a low-energy fracture in a COVID-negative patient without any preoperative respiratory symptoms or illness.

Pathogenesis of COVID-19: Hyperinflammation and Thromboembolic Disease

The clinical presentation of COVID-19 resembles viral pneumonia, with severe cases rapidly progressing to ARDS.¹⁹ CRS is implicit in the pathogenesis of these severe cases of COVID-19. Although the full immunologic response elicited by COVID-19 is still not fully elucidated, current reports indicate elevations of a distinct set of proinflammatory cytokines, including interleukin (IL)-2, IL-6, and tumor necrosis factor (TNF)- α .^{3,20} Treatment protocols for severe COVID-19 are aimed at attenuating this life-threatening inflammation, such as with the IL-6-inhibiting agent tocilizumab.^{3,20} These treatments are currently reserved for the population of patients with a declining clinical status paired with worsening inflammatory markers.³ The overwhelming inflammatory response in these

patients is believed to cause diffuse alveolar damage and endothelial dysfunction. The dysfunctional endothelium thus becomes prothrombotic, which predisposes patients to microangiopathy and microthrombi.^{5,20} The clinical implications of this are profound, as the presence of vasculitis and prothrombotic state can make patients vulnerable to pulmonary embolism, which can exacerbate hypoxemia caused by ARDS.⁵ This is a crucial point for consideration in asymptomatic COVID+ patients presenting with orthopaedic trauma, as we hypothesize that subclinical levels of systemic inflammation from COVID-19 may predispose to adverse outcomes. This theory is supported by a recent report out of Wuhan that has demonstrated alarmingly high mortality and ICU admission rates after elective surgery on asymptomatic patients in the incubation period of COVID-19.¹⁷

In addition to these microvascular aberrations, significant coagulation abnormalities appear to be associated with the CRS and implicated in disease progression.^{1,6,19,21,22} These hemostatic derangements include increased clot strength, increased fibrinogen and fibrin degradation product levels, elevated D-dimer levels, decreased prothrombin time and international normalized ratio times, as well as patterns of disseminated intravascular coagulation.^{21–23} Such changes also predispose these patients to thrombotic events such as venous thromboembolism, much like the previous zoonotic virus outbreaks [SARS and Middle East respiratory syndrome (MERS-CoV)].^{1,24} This is convincingly demonstrated by an amounting number of reported cases of young patients with large-vessel strokes as a presenting feature of COVID-19.²⁵ The most commonly observed hemostatic abnormality in these patients is elevated D-dimer levels (>1 $\mu\text{g/mL}$), which have specifically been associated with an increased risk of ICU admission, mechanical intubation requirement, and death.^{1,26} For these reasons, use of empiric anticoagulation at therapeutic doses on patients with highly elevated D-dimer levels is being implemented by some intensivists and is currently supported by some experts in the American College of Cardiology.¹ In fact, early reports have indicated decreased mortality in severe COVID-19 patients with coagulopathy who were treated with anticoagulation.²² It is possible that the coagulation abnormalities associated with this disease may



FIGURE 3. Products removed from percutaneous pulmonary suction embolectomy. The yellow products are presumed intramedullary fat, and the red products are the clot burden. Image quality is suboptimal because the camera was required to be in a plastic bag due to COVID+ status.

have contributed to the development of the acute DVTs in our patient, and that the intraoperative initiation of a heparin drip may have attenuated the effects of pulmonary emboli. These coagulative effects of COVID-19 and proposed benefits of anticoagulative therapies are important to consider when treating orthopaedic trauma patients.

In COVID+ patients presenting with orthopaedic trauma, the hyperinflammatory and hypercoagulable state caused by the virus may also have significant implications on blunt injury pathophysiology. After severe blunt trauma, damaged tissue induces a local and systemic inflammatory response mediated by the release of the cytokines TNF- α , IL-1 β , and, most importantly, IL-6. The severity of this inflammatory response and subsequent clinical course is determined by the following 3 factors: (1) the degree of the initial injury (“first hit”), (2) the individuals’ amounted biological response, and (3) the type of treatment (“second hit”).¹⁰ These 3 factors contribute toward an amounting inflammatory cascade that increases until a patient’s biologic reserve is overwhelmed, and a “tipping point” is reached (Fig. 4).¹⁰ The “tipping point” refers to a state of clinical instability associated with microvascular injury, interstitial edema, hemodynamic lability, and end-organ failure.¹⁰ The “first hit” can be reliably quantified in traumatized patients by measuring IL-6 levels, which have been shown to be correlated with increased incidence of multiple organ failure, and patient survival.²⁷ Emerging studies on COVID-19 have similarly observed correlations between IL-6 levels and disease severity, which suggests a potential mutual inflammatory pathway, with that of trauma patients (although stemming from a distinct inciting event).^{24,28} Therefore, COVID-19 may decrease a trauma patient’s biologic reserve before reaching a physiologic “tipping point” (Fig. 4). In other words, COVID-19 may unfavorably amplify the “first hit” by contributing a significant biologic response before the injury, whether the patient is symptomatic or not. This may manifest clinically as decreased cardiopulmonary capacity in these patients, albeit to variable extents based on the severity of their disease. This hypothesis is supported by a recent case series, demonstrating a 40% mortality rate in symptomatic COVID+ fracture patients.¹⁶

Among the 3 aforementioned factors contributing toward the “tipping point,” the treatment is the sole modifiable factor. In particular, long bone fractures treated with intramedullary fixation are at risk for fat embolization in addition to the inflammatory response from this “second

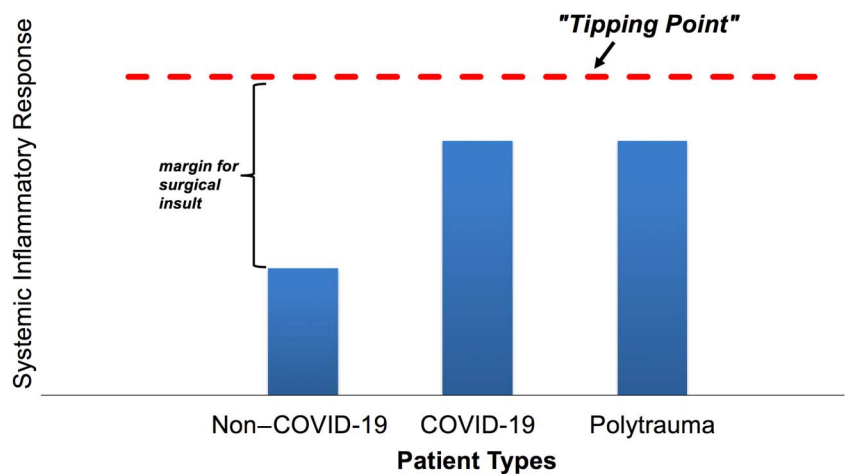


FIGURE 4. Diagram demonstrating different theoretical patients’ biologic reserves to withstand systemic inflammation before reaching a tipping point, characterized by clinical instability.

hit.”^{18,29} These events have been demonstrated to result in pulmonary insult, changes in markers of coagulation, and, at times, cardiovascular strain. The coagulative effects are due to simultaneous activation of both the fibrinolytic and coagulation pathways,^{29,30} and the inflammatory effects are mediated by IL-6.³⁰ As for the cardiopulmonary effects of intramedullary fixation, intraoperative measurements on humans using transesophageal echocardiogram and cardiopulmonary monitoring have demonstrated consistent pulmonary arterial pressure elevations, and in severe cases—significant hypoxemia and right heart strain, during guide-wire insertion and canal reaming.^{29,31} These findings are mostly attributable to fat emboli, which occur in approximately 90% of trauma patients but are only clinically apparent in 1%–5%.³¹ In addition, ARDS is a potential consequence of the inflammatory response from intramedullary fixation of femur fractures.^{11,32}

Current Outcomes Data

In the aforementioned study on elective surgery outcomes of asymptomatic COVID+ patients, they reported a 44.1% (15 of 34) ICU admission rate postoperatively, which is significantly higher than the reported 26.1% in hospitalized nonsurgical COVID-19 patients.¹⁷ Furthermore, the reported 20.5% (7 of 34) mortality rate was significantly higher than the overall case-fatality rate of 2.3% in nonsurgical COVID-19 patients.³³ Patients in that study also developed COVID symptoms on average 2.6 days postoperatively, and the median time from symptom onset to the development of dyspnea was 3.5 days. In comparison, a previous study on nonsurgical COVID-19 patients reported that the median time for symptom onset was 8.0 days.¹⁹ The difference is alarming. The most common postsurgical complication in the ICU-admitted patients in that study was ARDS, and over half of these patients received subsequent immunosuppressive medications to attenuate the diseases’ inflammatory response. The authors of this study reached a similar conclusion as ours that surgical stress occurring during the incubation period of SARS-CoV-2 infection exacerbates disease progression and severity.¹⁷

Another recent study out of China by Mi et al¹⁶ reported on 10 COVID+ fracture patients, 3 of which did not have any signs or symptoms of the disease. Three patients underwent surgical fixation of their fractures, and the rest were treated nonoperatively because of their declining clinical status. They reported that 4 of these 10 patients died at 8 and 14 days after admission. Abnormal D-dimer levels were present in all patients, elevated CRP in 90% of patients, but normal prothrombin times in 70% of patients.¹⁶ The authors of this study also concluded that the characteristics and prognosis of COVID-19 patients with fractures tend to be more severe than those reported for COVID+ patients without fractures.¹⁶

Most recently, Catellani et al³⁴ published their outcomes in Italy on the treatment of proximal femoral fragility fractures in patients with COVID-19. They reported on 16 symptomatic COVID+ patients with confirmed viral pneumonia on chest computed tomography. Three of these patients died of respiratory failure before surgery, the remaining 13 series underwent surgical stabilization of their fractures with

either an intramedullary nail or hemiarthroplasty. Nine of these patients were stable postoperatively, whereas 4 patients died of respiratory failure on the first, third, and seventh day postoperatively.³⁴ The authors of this study concluded that surgical stabilization of proximal femoral fractures resulted in stabilization of respiratory parameters but did mention that elderly patients with comorbidities and symptomatic COVID-19 are not eligible for orthopaedic surgery.³⁴

SUMMARY AND RICH FUTURE DIRECTIONS

The current environment in the health care system is unprecedented. There are little to no data to guide us in our decision making when treating patients with COVID-19. The disease manifests in ways we would have never been able to predict. The level of cytokine response, hypercoagulability, and pulmonary dysfunction associated with the COVID-19 virus may predispose to a catastrophic “second hit” after even low-energy trauma. This is in line with the previous hypotheses that postsurgical complications are more accurately predicted by assessing objective data covering several physiological systems (coagulation, acid–base changes, soft-tissue damage, etc.) compared with using data from a single physiologic system (eg, acidemia).³⁵ Regarding our patient, we hypothesize that COVID-19 may have lowered her physiologic reserves to withstand the relatively low intraoperative embolus burden. Interestingly, not only did the clot burden fail to correlate with the patient’s physiologic status after nailing, she did not show any significant improvement after embolectomy of the thrombus and fat, indicating another disease process such as ARDS.

CONSIDERATIONS FOR PATIENTS WITH COVID-19 SUSTAINING ORTHOPAEDIC TRAUMA

The following precautions may be appropriate when dealing with unprecedented challenges associated with COVID-19 patients presenting with orthopaedic trauma injuries.

1. Test for COVID-19 in all patients with unknown disease status upon admission.
2. Consider obtaining baseline inflammatory markers including IL-6 (if available), D dimer, and CRP, which may aid in surgical decision making and prognosis.
3. Consider obtaining lower extremity duplex ultrasound in all patients testing positive for COVID-19 and high-risk fractures.
4. For patients with confirmed proximal DVT, consider either aggressive intraoperative anticoagulation or placement of an inferior vena cava filter preoperatively.
5. Consider alternative orthopaedic trauma management strategies (eg, damage control orthopaedics and nonoperative treatment) in patients with severe cases of symptomatic COVID-19, even in low-energy trauma.
6. Consider surgical treatments that avoid canal instrumentation.
7. Consider avoiding excessive reaming if intramedullary fixation is performed.

CONCLUSION

Mounting evidence suggests that the pathogenesis of COVID-19 involves a hyperinflammatory response predisposing patients to thromboembolic disease and acute respiratory distress. In the setting of severe blunt trauma, damaged tissues induce a local and systemic inflammatory response through similar pathways to COVID-19. As such, patients with COVID-19 sustaining orthopaedic trauma injuries may have an amplified response to the traumatic insult because of their baseline hyperinflammatory and hypercoagulable states. Careful consideration and risk/benefit analysis, including preoperative evaluation of systemic inflammation and respiratory status, is paramount in patients with COVID-19 presenting with orthopaedic trauma injuries.

REFERENCES

- Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. *J Am Coll Cardiol*. 2020. [epub ahead of print]. doi:10.1016/j.jacc.2020.04.031.
- Organization WH. *Coronavirus Disease 2019 (COVID-19): Situation Report. 72*. Geneva, Switzerland: World Health Organization; 2020.
- Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395:1033–1034.
- Shi Y, Wang Y, Shao C, et al. COVID-19 infection: the perspectives on immune responses. *Cell Death Differ*. 2020;27:1451–1454.
- Liu PP, Blet A, Smyth D, et al. The science underlying COVID-19: implications for the cardiovascular system. *Circulation*. 2020. doi:10.1161/circulationaha.120.047549.
- Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382:1708–1720.
- Gong J, Dong H, Xia SQ, et al. Correlation analysis between disease severity and inflammation-related parameters in patients with COVID-19 pneumonia. *medRxiv*. 2020. [epub ahead of print]. doi:10.1101/2020.02.25.20025643.
- Moore FA, Moore EE. Evolving concepts in the pathogenesis of post-injury multiple organ failure. *Surg Clin North Am*. 1995;75:257–277.
- Keel M, Trentz O. Pathophysiology of polytrauma. *Injury*. 2005;36:691–709.
- Pape HC, Giannoudis P, Krettek C. The timing of fracture treatment in polytrauma patients: relevance of damage control orthopedic surgery. *Am J Surg*. 2002;183:622–629.
- Lasanianos NG, Kanakaris NK, Giannoudis PV. Intramedullary nailing as a “second hit” phenomenon in experimental research: lessons learned and future directions. *Clin Orthop Relat Res*. 2010;468:2514–2529.
- Giannoudis PV, Smith RM, Bellamy MC, et al. Stimulation of the inflammatory system by reamed and unreamed nailing of femoral fractures. An analysis of the second hit. *J Bone Joint Surg Br*. 1999;81:356–361.
- Roberts CS, Pape HC, Jones AL, et al. Damage control orthopaedics: evolving concepts in the treatment of patients who have sustained orthopaedic trauma. *Instr Course Lect*. 2005;54:447–462.
- Giannoudis PV, Giannoudis M, Stavlas P. Damage control orthopaedics: lessons learned. *Injury*. 2009;40(Suppl 4):S47–S52.
- Kalinterakis G, Koutras A, Syllaios A, et al. The evolution and impact of the “damage control orthopaedics” paradigm in combat surgery: a review. *Eur J Orthop Surg Traumatol*. 2019;29:501–508.
- Mi B, Chen L, Xiong Y, et al. Characteristics and early prognosis of COVID-19 infection in fracture patients. *J Bone Joint Surg Am*. 2020. [epub ahead of print]. doi:10.2106/jbjs.20.00390.
- Lei S, Jiang F, Su W, et al. Clinical characteristics and outcomes of patients undergoing surgeries during the incubation period of COVID-19 infection. *EClinicalMedicine*. 2020:100331. [epub ahead of print]. doi:10.1016/j.eclinm.2020.100331.
- Giannoudis PV, van Griensven M, Hildebrand F, et al. Femoral nailing-related coagulopathy determined by first-hit magnitude: an animal study. *Clin Orthop Relat Res*. 2008;466:473–480.
- Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497–506.
- Liu B, Li M, Zhou Z, et al. Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? *J Autoimmun*. 2020:102452. [epub ahead of print]. doi:10.1016/j.jaut.2020.102452.
- Ranucci M, Ballotta A, Di Dedda U, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. *J Thromb Haemost*. 2020. [epub ahead of print]. doi:10.1111/jth.14854.
- Tang N, Bai H, Chen X, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020;18:1094–1099.
- Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395:507–513.
- Chen X, Zhao B, Qu Y, et al. Detectable serum SARS-CoV-2 viral load (RNAemia) is closely correlated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients. *Clin Infect Dis*. 2020. [epub ahead of print]. doi:10.1093/cid/ciaa449.
- Oxley TJ, Mocco J, Majidi S, et al. Large-vessel stroke as a presenting feature of covid-19 in the young. *N Engl J Med*. 2020;382:e60.
- Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054–1062.
- Cuschieri J, Bulger E, Schaeffer V, et al. Early elevation in random plasma IL-6 after severe injury is associated with development of organ failure. *Shock*. 2010;34:346–351.
- Luo P, Liu Y, Qiu L, et al. Tocilizumab treatment in COVID-19: a single center experience. *J Med Virol*. 2020. [epub ahead of print]. doi:10.1002/jmv.25801.
- Robinson CM, Ludlam CA, Ray DC, et al. The coagulative and cardio-respiratory responses to reamed intramedullary nailing of isolated fractures. *J Bone Joint Surg Br*. 2001;83:963–973.
- Husebye EE, Opdahl H, Røise O, et al. Coagulation, fibrinolysis and cytokine responses to intramedullary nailing of the femur: an experimental study in pigs comparing traditional reaming and reaming with a one-step reamer-irrigator-aspirator system. *Injury*. 2011;42:630–637.
- Rudloff MI, Smith WR. Intramedullary nailing of the femur: current concepts concerning reaming. *J Orthop Trauma*. 2009;23(5 Suppl):S12–S17.
- Pape HC, Aufm’Kolk M, Paffrath T, et al. Primary intramedullary femur fixation in multiple trauma patients with associated lung contusion—a cause of posttraumatic ARDS? *J Trauma*. 1993;34:540–547; discussion 547–548.
- Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323:1239–1242.
- Catellani F. Treatment of proximal femoral fragility fractures in patients with COVID-19 during the SARS-CoV-2 outbreak in Northern Italy. *J Bone Joint Surg Am*. 2020. [epub ahead of print]. doi:10.2106/JBJS.20.00617.
- Halvachizadeh S, Baradaran L, Cinelli P, et al. How to detect a polytrauma patient at risk of complications: a validation and database analysis of four published scales. *PLoS One*. 2020;15:e0228082.