Ref: Ro J Med Pract. 2022;17(4)
DOI: 10.37897/RJMP.2022.4.5

# Venous thromboembolism in burn patients – low incidence or underdiagnosis?

Mirela TIGLIS[1], Ileana PERIDE[2], Tiberiu Paul NEAGU[3], Andrei NICULAE[2], Ioan LASCAR[3]

[1]Department of Anesthesia and Intensive Care, Emergency Clinical Hospital of Bucharest, Romania
[2]Department of Nephrology, "Carol Davila" University of Medicine and Pharmacy Bucharest, Romania
[3]Department of Plastic Surgery and Reconstructive Microsurgery,
"Carol Davila" University of Medicine and Pharmacy Bucharest, Romania

## Abstract

*Venous thromboembolism (VTE), essentially deep venous thrombosis and pulmonary embolism, urinary tract infection, and renal failure are the main unplanned hospital events with negative long-term impact on burn patients' rehabilitation. Due to the hypercoagulable state induced by severe critical burns, either in the acute or recovery phase and the intimal vascular damage, the risk of VTE is increased, with an incidence varying from 0.4% to almost 60%. Other risk factors for VTE in burn patients are prolonged immobilization, long and multiple surgical interventions, central venous catheterization, wound infection and sepsis, extensive burns, and red blood cell transfusion. To avoid underdiagnosing VTE, in face of increased incidence of asymptomatic venous thromboembolism, high risk-patients should be routinely screened using Doppler ultrasound. Patients' weight and burn size, as well as the high incidence of heparin resistance in the first weeks after injury, should be considered when establishing the optimal dose for venous thromboembolism prophylaxis, targeting an anti-Xa level of 0.2-0.5 IU/mL.*

**Keywords:** deep venous thromboembolism, venous thromboembolism, burns, altered pharmacokinetics, hypercoagulability

## INTRODUCTION

In the last years, venous thromboembolism (VTE), as deep venous thrombosis (DVT) and pulmonary embolism (PE), raised various problems in burn patients, category at the highest risk, but it remains a controversial subject to be studied [1]. Nowadays, it is considered not to have a low incidence, but to be partly underdiagnosed, since almost 50% of cases are asymptomatic ("*silent VTE*") [2,3]. VTE (DVT/PE), along with urinary tract infection and renal failure are the main unplanned hospital negative events influencing the long-term quality of life in patients suffering severe burns [4].

Reports show an incidence of VTE in burn patients ranging from 0.4-0.8% [5,6], to 5.92% [7] or 8% [8] to as high as 53% [9]. When prophylaxis methods are not used, the rate of venous thromboembolism rises to 60% [10]. An interesting study, including 233 autopsies of burn patients, showed that PE was the cause of death in less than 1% of cases, but subclinical VTE was found in 25% of cases [11]. It appears that studies that focus only on clinical manifestations report a low incidence, while in those in which various diagnostic techniques are used, such as ultrasound, the noted incidence is higher [12].

The main problems with identifying VTE in burn patients are represented by:

- the high number of hospitalized patients with asymptomatic DVT [13];

*Corresponding authors:*
Tiberiu Paul Neagu
*E-mail:* dr.neagupaul@gmail.com

*Article History:*
Received: 26 December 2022
Accepted: 30 December 2022

- low-sensitive diagnostic tools [14,15];
- burns mimicking the main symptoms of DVT, especially if lower limbs are involved (pain, swelling, redness, tenderness) [7].

## RISK FACTORS FOR VENOUS THROMBOEMBOLISM

Patients presenting critical burns are at risk of developing venous thromboembolism (VTE), like patients with major traumas, and effective mechanical and pharmacological prophylaxis should be applied [1].

In Figure 1 are presented the main risk factors for VTE in patients with severe burns, factors whose presence places patients in the high-risk category for thromboembolic events [1,16-19]. In the acute phase after a burn injury, there is a systemic hypermetabolic response, being responsible for a hyperdynamic state, increased basal energy expenditure and improper protein catabolism, along with an inadequate immune response [20]. In a large prospective clinical trial, Jeschke et al. detailed the postburn pathophysiologic response, showing that in this period, patients have the highest risk of developing DVT, associating increased morbidity [21]. It is mainly due to the hypercoagulable state during the recovery period [6]. Almost 3% of burn deaths are caused by thromboembolic complications [22].

Various reports presented numerous other risk factors for this subgroup of patients, including the presence of inhalation injury, larger and deeper burned areas, long and complicated surgical interventions, older age, obesity, increased days of mechanical ventilation, central venous catheters' presence, pneumonia development, and extended ICU (intensive care unit) hospitalization [8,9,23,24]. Extensive burns, associated trauma of the lower limbs, along with wound infections are considered to put the patient at risk of developing DVT [1]. Further, Mullins et al., in a retrospective study from a burn center including 1452 adult patients with acute burns, presented additional factors predisposing to DVT development, like male sex, smoking, alcoholic status, and increased number of transfusions [7]. Wibbenmeyer et colab. emphasized the need for VTE prophylaxis in patients receiving transfusion-packed red blood cells (>4 units) [25]. Black race, mechanical ventilation, and history of VTE are additional risk factors, doubling the incidence of venous thromboembolism [6].

Pannucci et al., in a retrospective study including 19 cases, showed that in patients with thermal injury, there are some acquired, in-hospital risk factors for VTE. The number of surgical interventions, pneumonia presence, and central venous catheters significantly increase the risk of thromboembolic events [19]. Younger patients presenting burns affecting 45-55% TBSA (total body surface area) are prone to develop VTE, as shown by Ahuja et colab. [8].

## SCREENING AND PROPHYLACTIC METHODS

There are some concerns about routine VTE prophylaxis in burn patients, like the risk of bleeding (especially in patients needing multiple surgical interventions), or heparin-induced thrombocytopenia (HIT) appearance [5,6,26]. A recent meta-analysis, encompassing 44 randomized controlled trials (90.095 patients), presented the superiority of low-molecular-weight heparin in preventing VTE, having the lowest risk of hemorrhagic events compared to other agents [27].

Various studies emphasized the need for dose-adjusted DVT pharmacologic agents used for prophylaxis in burn patients (increased doses) due to burn-induced altered pharmacokinetics. Therefore, monitoring anti-factor Xa levels, in patients receiving low molecular-weight heparin (LMWH) helps achieve optimal dosages [28,29]. In a study including 64 patients with acute burns, Faraklas et al. showed that the enoxaparin dosage used for prophylaxis in burn patients in influenced not only by the patient weight, but also by burn size, and routine use of standard dosages is not recommended. The monitoring of anti-Xa (AFXa) levels is of paramount importance [22,30]. Normally, an anti-Xa level >0.2 IU/mL (0.2-0.5 IU/mL) ensures optimal prophylaxis [31]. As a recent study showed, it is of paramount importance in obese patients [32]. Nevertheless, Cato et

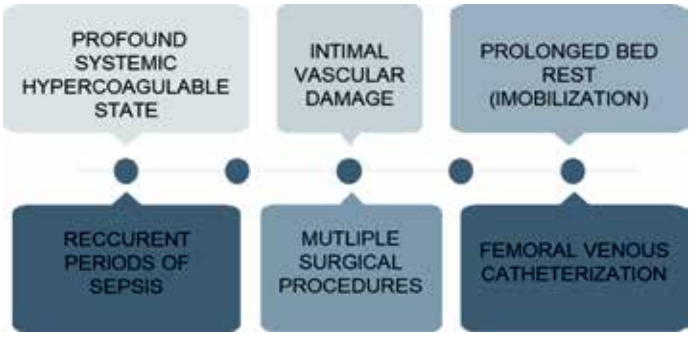


***FIGURE 1.*** *The main risk factors for venous thromboembolism in burn patients*

***TABLE 1.*** *The Caprini risk assessment model*
*(*adapted after Caprini JA. Thrombosis risk assessment as a guide to quality patient care. Dis Mon. 2005 Feb-Mar;51(2-3):70-8.)*

| **1 POINT FOR EACH FACTOR** | **2 POINTS FOR EACH FACTOR** | **3 POINTS FOR EACH FACTOR** |
|---|---|---|
| age 40-59 years<br>minor surgery<br>swollen legs<br>varicose veins<br>BMI ≥25<br>medical patient at bed rest<br>history of prior major surgery (<1 month)<br>sepsis (<1 month)<br>acute myocardial infarction (<1 month)<br>congestive heart failure (<1 month)<br>abnormal pulmonary function (COPD)<br>history of IBD | age 60-74 years<br>present cancer (except breast and thyroid)<br>prior cancer (except non-melanoma skin cancer)<br>confined to bed >72 hours<br>immobilizing plaster cast<br>central venous access<br>laparoscopic surgery (>45 minutes)<br>major open surgery (>45 minutes)<br>arthroscopic surgery | age > 75 years<br>history of VTE<br>familial history of VTE<br>**++** prothrombin 20210A<br>**++** factor V Leiden<br>**++** lupus anticoagulant<br>HIT<br>á anticardiolipin<br>á serum homocysteine<br>congenital / acquired thrombophilias |
| **5 POINTS FOR EACH FACTOR** | **1 POINT FOR EACH FACTOR (women only)** | **Caprini risk category** |
| major surgery (>6 hours)<br>elective major lower extremity arthroplasty<br>hip, pelvis, leg fracture (<1 month)<br>polytrauma (<1 month)<br>acute spinal cord fracture or paralysis (<1 month)<br>stroke (<1 month) | pregnant<br>post-partum (<1 month)<br>history of unexplained / recurrent abortion (≥3)<br>oral contraceptives<br>hormone replacement therapy | ***Total score*** / ***Risk***<br>0-4 points / low<br>5-8 points / moderate<br>≥9 points / high |

*Note: BMI=body mass index; COPD=chronic obstructive pulmonary disease; IBD=inflammatory bowel disease; VTE=venous thromboembolism; HIT=heparin-induced thrombocytopenia*

al. concluded in a recent study that it must always be kept in mind the high incidence of heparin-resistance 2 weeks after a burn injury and how it influences the anticoagulant effect of heparin [33]. As Meizoso et colab. suggested, considering the incidence of VTE in patients receiving proper enoxaparin dosage for prophylaxis, as defined by anti-Xa levels, the role of antiplatelet agents use should be studied [24].

Van Haren et al. studied hypercoagulability development after burn injury using thrombelastography (TEG), emphasizing that most burn patients have normal coagulation parameters at admission, being hypercoagulable during the recovery phase. But there are patients presenting with a hypercoagulable state during the initial phase, and those are predisposed to VTE [34].

France Society of Anesthesia and Intensive Care published in 2020 a guideline regarding severe thermal burn management. As for thromboprophylaxis, experts stated that it should be routinely used for patients presenting with severe burn in the initial phase, as well as mechanical methods (like intermittent pneumatic compression devices) for the unburned areas if heparin is contraindicated, and early ambulation [35-37]. Doppler ultrasound appears to be the most suitable method for screening and diagnosing venous thromboembolism [8].

The Caprini risk assessment model (Table 1) is used for predicting VTE in medical and surgical patients and it is widely used, with score values ≥10 points suggesting the existence of a high risk for thromboembolic complications [37,38]. It is also useful for burn patients [39]. A study including 304 burn patients stated that, for patients presenting with burns, this score should be calculated by adding the presence of electrical burn injuries [40].

## CONCLUSION

Burn patients are at risk of developing deep venous thrombosis of pulmonary embolism, with an incidence reaching 60% when prophylactic measures are not used. The most incriminated risk factors are the hypercoagulable state and intimal vascular damage, heparin resistance, prolonged immobilization, long and multiple surgical interventions, central venous catheterization, wound infection and sepsis, extensive burns, and red blood cell transfusion. Other factors are older age, male sex, obesity, inhalational injury, pneumonia, and mechanical ventilation. We consider that to avoid underdiagnosing VTE, in face of increased incidence of asymptomatic episodes, high risk-patients should be routinely screened using Doppler ultrasound.

*Conflict of interest:* none declared
*Financial support:* none declared

## REFERENCES


1. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ; American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012 Feb;141(2 Suppl):7S-47S.
2. Sikora S, Papp A. Venous thromboembolism in burn patients is not prevented by chemoprophylaxis. *Burns*. 2017 Sep;43(6):1330-4.
3. Boersma RS, Jie KS, Verbon A, van Pampus EC, Schouten HC. Thrombotic and infectious complications of central venous catheters in patients with hematological malignancies. *Ann Oncol*. 2008 Mar;19(3):433-42.
4. Deeter L, Seaton M, Carrougher GJ, McMullen K, Mandell SP, Amtmann D, Gibran NS. Hospital-acquired complications alter quality of life in adult burn survivors: Report from a burn model system. *Burns*. 2019 Feb;45(1):42-7.
5. Rue LW 3rd, Cioffi WG Jr, Rush R, McManus WF, Pruitt BA Jr. Thromboembolic complications in thermally injured patients. *World J Surg*. 1992 Nov-Dec;16(6):1151-4; discussion 1155.
6. Satahoo SS, Parikh PP, Naranjo D, Davis JS, Duncan RC, Pizano LR et al. Are burn patients really at risk for thrombotic events? *J Burn Care Res*. 2015 Jan-Feb;36(1):100-4.
7. Mullins F, Mian MA, Jenkins D, Brandigi C, Shaver JR, Friedman B et al. Thromboembolic complications in burn patients and associated risk factors. *J Burn Care Res*. 2013 May-Jun;34(3):355-60.
8. Ahuja RB, Bansal P, Pradhan GS, Subberwal M. An analysis of deep vein thrombosis in burn patients (Part 1): Comparison of D-dimer and Doppler ultrasound as screening tools. *Burns*. 2016 Dec;42(8):1686-92.
9. Mayou BJ, Wee J, Girling M. Deep vein thrombosis in burns. *Burns* 1981;7:438–40.
10. Geerts WH, Code KI, Jay RM, Chen E, Szalai JP. A prospective study of venous thromboembolism after major trauma. *N Engl J Med*. 1994 Dec 15;331(24):1601-6.
11. Foley FD, Moncrief JA, Mason AD Jr. Pathology of the lung in fatally burned patints. *Ann Surg*. 1968 Feb;167(2):251-64.
12. Ball RL, Keyloun JW, Brummel-Ziedins K, Orfeo T, Palmieri TL, Johnson LS et al. Burn-Induced Coagulopathies: a Comprehensive Review. *Shock*. 2020 Aug;54(2):154-67.
13. Geerts WH, Heit JA, Clagett GP, Pineo GF, Colwell CW, Anderson FA Jr, Wheeler HB. Prevention of venous thromboembolism. *Chest*. 2001 Jan;119(1 Suppl):132S-175S.
14. Faucher LD, Conlon KM. Practice guidelines for deep venous thrombosis prophylaxis in burns. *J Burn Care Res*. 2007 Sep-Oct; 28(5):661-3.
15. ISBI Practice Guidelines Committee; Advisory Subcommittee; Steering Subcommittee. ISBI Practice Guidelines for Burn Care, Part 2. *Burns*. 2018 Nov;44(7):1617-706.
16. Pannucci CJ, Obi AT, Timmins BH, Cochran AL. Venous Thromboembolism in Patients with Thermal Injury: A Review of Risk Assessment Tools and Current Knowledge on the Effectiveness and Risks of Mechanical and Chemical Prophylaxis. *Clin Plast Surg*. 2017 Jul;44(3):573-81.
17. Tracy LM, Cameron PA, Singer Y, Earnest A, Wood F, Cleland H, Gabbe BJ. Venous thromboembolism prophylaxis practice and its association with outcomes in Australia and New Zealand burns patients. *Burns Trauma*. 2021 Feb 11;9:tkaa044.
18. Abedi N, Papp A. A survey of current practice patterns in prophylaxis against venous thromboembolism (VTE) and gastrointestinal (GI) ulceration among Canadian burn centers. *Burns*. 2011 Nov;37(7):1182-6.
19. Pannucci CJ, Osborne NH, Park HS, Wahl WL. Acquired inpatient risk factors for venous thromboembolism after thermal injury. *J Burn Care Res*. 2012 Jan-Feb; 33(1):84-8.
20. Berndtson AE, Costantini TW, Smith AM, Kobayashi L, Coimbra R. Does sex matter? Effects on venous thromboembolism risk in screened trauma patients. *J Trauma Acute Care Surg*. 2016 Sep;81(3):493-9.
21. Jeschke MG, Chinkes DL, Finnerty CC, Kulp G, Suman OE, Norbury WB et al. Pathophysiologic response to severe burn injury. *Ann Surg*. 2008 Sep;248(3):387-401.
22. Blake M, Roadley-Battin R, Torlinski T. Prophylactic anti-coagulation after severe burn injury in critical care settings. *Acta Med Litu*. 2019;26(1):38-45.
23. Sheridan RL, Rue LW 3rd, McManus WF, Pruitt BA Jr. Burns in morbidly obese patients. *J Trauma*. 1992 Dec;33(6):818-20.
24. Meizoso JP, Ray JJ, Allen CJ, Van Haren RM, Ruiz G, Namias N et al. Hypercoagulability and venous thromboembolism in burn patients. *Semin Thromb Hemost*. 2015 Feb;41(1):43-8.
25. Wibbenmeyer LA, Hoballah JJ, Amelon MJ, Chang PX, Loret De Mola RM, Lewis RD 2nd et al. The prevalence of venous thromboembolism of the lower extremity among thermally injured patients determined by duplex sonography. *J Trauma*. 2003 Dec;55(6):1162-7.
26. Fecher AM, O'Mara MS, Goldfarb IW, Slater H, Garvin R, Birdas TJ, Caushaj PF. Analysis of deep vein thrombosis in burn patients. *Burns*. 2004 Sep;30(6):591-3.
27. Eck RJ, Elling T, Sutton AJ, Wetterslev J, Gluud C, van der Horst ICC et al. Anticoagulants for thrombosis prophylaxis in acutely ill patients admitted to hospital: systematic review and network meta-analysis. *BMJ*. 2022 Jul 4;378:e070022.
28. Cronin BJ, Godat LN, Berndtson AE, Pham A, Kolan S, Box K et al. Anti-Xa guided enoxaparin dose adjustment improves pharmacologic deep venous thrombosis prophylaxis in burn patients. *Burns*. 2019 Jun;45(4):818-24.
29. Lin H, Faraklas I, Saffle J, Cochran A. Enoxaparin dose adjustment is associated with low incidence of venous thromboembolic events in acute burn patients. *J Trauma*. 2011 Dec;71(6):1557-61.
30. Faraklas I, Ghanem M, Brown A, Cochran A. Evaluation of an enoxaparin dosing calculator using burn size and weight. *J Burn Care Res*. 2013 Nov-Dec;34(6):621-7.
31. Wei MY, Ward SM. The Anti-Factor Xa Range For Low Molecular Weight Heparin Thromboprophylaxis. *Hematol Rep*. 2015 Nov 23;7(4):5844.
32. McKinzie BP, Nizamani R, Jones S, King B, Williams FN. Single-center Experience with Venous Thromboembolism Prophylaxis for Obese Burn Patients. *J Burn Care Res*. 2021 May 7;42(3):365-8.
33. Cato LD, Bailiff B, Price J, Ermogeneous C, Hazeldine J, Lester W et al. Heparin resistance in severe thermal injury: A prospective cohort study. *Burns Trauma*. 2021 Oct 20;9:tkab032.
34. Van Haren RM, Thorson CM, Valle EJ, Busko AM, Guarch GA, Andrews DM et al. Hypercoagulability after burn injury. *J Trauma Acute Care Surg*. 2013 Jul;75(1):37-43; discussion 43.
35. Legrand M, Barraud D, Constant I, Devauchelle P, Donat N, Fontaine M et al. Management of severe thermal burns in the acute phase in adults and children. *Anaesth Crit Care Pain Med*. 2020 Apr;39(2):253-67.
36. AlHarbi M, AlKouny A, Ahmed A, Hazazi B. Pulmonary embolism in anticoagulated burn patient: A case report. *Saudi J Anaesth*. 2021 Oct-Dec;15(4):444-6.
37. Caprini JA. Thrombosis risk assessment as a guide to quality patient care. *Dis Mon*. 2005 Feb-Mar;51(2-3):70-8.
38. Golemi I, Salazar Adum JP, Tafur A, Caprini J. Venous thromboembolism prophylaxis using the Caprini score. *Dis Mon*. 2019 Aug;65(8):249-98.
39. Li Q, Ba T, Wang LF, Chen Q, Li F, Xue Y. Stratification of venous thromboembolism risk in burn patients by Caprini score. *Burns*. 2019 Feb;45(1):140-5.
40. Althunayan TA, AlQarni SM, Mohsenh WA, Alkhalifah AM, Alsadi AN, Alrushid OS, Al-Qattan MM. Risk factors for thromboembolism in burn patients admitted to the burn unit at King Abdulaziz Medical City, Riyadh, Kingdom of Saudi Arabia. *Saudi Med J*. 2019 Oct;40(10):1027-31.