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CUSHING'S SYNDROME, A RISK FACTOR FOR VENOUS THROMBOEMBOLISM IS A CANDIDATE FOR GUIDELINES

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Abstract

Objectives. The present paper aims to review important contemporary information about VTE risk in endogenous and exogenous CS, as a substantial discrepancy exists between the results of a recent meta-analysis confirming the increased risk for VTE and the absence of CS in VTE guidelines.

Methods. An extensive search of relevant databases (e.g. PubMed, Google Scholar, and Scopus) was performed in order to establish the interconnectedness of the following terms: Cushing's syndrome, venous thromboembolism, deep vein thrombosis, pulmonary embolism.

Results. The analysis demonstrated that patients with CS have about ten times the risk for VTE, particularly during the first year following the diagnosis of CS. Oral glucocorticoid users (with iatrogenic CS) have a 3-fold increase in risk of VTE in comparison with non-users. The most recent 2019 meta-analysis encompassed 7142 patients with endogenous CS (including Cushing's disease) undergoing transsphenoidal surgery or adrenalectomy, and their risk of unprovoked VTE was almost 18 times higher in comparison with a healthy population.

Conclusion. Over the past 50 years considerable evidence of increased VTE risk in CS has been accumulated. It pertains to both endogenous and exogenous type of CS and has been confirmed in the vast majority, if not all the available studies, including meta-analyses. Nevertheless, official CS guidelines make no mention of CS as a VTE risk factor, even though it is important that not only physicians who treat CS, but also physicians who manage patients with suspected VTE be aware of increased VTE risk.

Keywords: Cushing's syndrome, venous thromboembolism, deep vein thrombosis, pulmonary embolism, guidelines.

INTRODUCTION

Cushing's disease and Cushing's syndrome (CS) are recognized as having high cardiovascular risk (1-3). Patients with Cushing's disease and CS have higher incidence and/or prevalence of numerous cardiovascular diseases and conditions: obesity, arterial hypertension, left ventricular hypertrophy, diabetes mellitus, dyslipidemia, metabolic syndrome, coronary artery disease including myocardial infarction (MI), heart failure (HF), venous thromboembolism (VTE), sleep apnea syndrome, and non-alcoholic fatty liver disease (2,4-6). The increased risk for VTE in CS was recognized half a century ago (7-9). Numerous papers confirm this association between VTE and Cushing's disease/CS (1,10-14). The aim of the paper is to review important contemporary information about VTE risk in endogenous and exogenous CS.

METHODS

In view of a meta-analysis published in 2019 (1), the aim of this paper is to perform a narrative review of the topic, encompassing meta-analyses, registries, consensus statements, individual studies, and VTE guidelines. For the purpose of this paper, we searched through relevant databases such as PubMed, Google Scholar, Scopus, Science Direct, Springer, and Wiley. The following terms were searched for: Cushing and Cushing's syndrome or Cushing and Cushing's disease, combined with venous thromboembolism, deep vein thrombosis, pulmonary embolism, pulmonary thromboembolism. Only articles written in English were considered. No time limits were used.

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RESULTS

Incidence of VTE in CS

VTE is not a rare finding in CS, particularly in those individuals who underwent surgery and/or selective venous sampling (15,16). Patients with CS have about ten times the risk of developing VTE, especially during the first year following the diagnosis of CS (17,18). Interestingly, the elevated risk for HF and VTE in CS may be transient, while the risk for MI seems to be permanently elevated (18). Users of oral glucocorticoids have a 3-fold increase in risk of VTE compared to non-users (19). A meta-analysis of 37 studies showed that patients with CS who undergo surgery have increased risk for VTE compared to those without CS. Patients with CS have a 3-fold higher risk for VTE compared to non-CS individuals (20). A high level of glucocorticoids in CS leads to a hypercoagulable state, which then raises the likelihood of pulmonary thromboembolism (PTE) and deep vein thrombosis (DVT). The hypercoagulable state is also linked to higher mortality in these patients (13,21,22).

Individual studies of VTE in CS

In a study done by Stuijver *et al.*, which included 473 patients with CS, 360 of whom suffered from ACTH-dependent pituitary CS, the incident rate for first-ever VTE prior treatment was 12.9% per persons-years. This study showed that patients with CS who had undergone pituitary surgery are at high risk for VTE. Namely, the risk of postoperative VTE in Cushing's disease patients who underwent transsphenoidal surgery was 3.4%, whereas no VTE was observed in the control group. However, none of almost 200 patients who underwent transsphenoidal surgery due to nonfunctioning pituitary adenomas developed VTE. The fact that postoperative VTE occurred only in ACTH-dependent CS raises the question of whether this happens because of postoperative variation in cortisol levels or due to ACTH mediated influence on hemostatic parameters (10).

Manetti *et al.* showed that patients with CS have increased levels of hemostatic factors (12). It seems reasonable that this alteration in coagulation indexes can lead to VTE. This is why these authors suggest performing the evaluation of hemostatic and fibrinolytic agents in patients with CS (12). The group of 6550 VTE patients was compared to 10,000 controls (matched for age and gender) and current oral glucocorticoid therapy was associated with 3-fold greater risk (19). Systemic glucocorticoids increase the risk of VTE among present and recent but not among former users, as demonstrated in Danish Nationwide (5.6 million citizens) Population-Based Study (3). Interestingly, in patients who were taking oral glucocorticoids, the risk for PTE was more pronounced as compared to DVT (3). It seems that the risk of VTE in glucocorticoid users decreases with prolonged duration of use (19). For example, admission because of VTE within 2 months following hospital discharge was 4.1 times higher in glucocorticoid users (23). On the other hand, users of inhaled or intestinal acting glucocorticoids showed persisted but less prominent increased risk for VTE (3,20). Moreover, glucocorticoid therapy is associated with a 2-fold higher risk of VTE among the outpatients (24). In a study by Babic *et al.* 7.4% of 4,217 patients had CS. The VTE incidence rates were almost 3 times higher in patients with CS. This raises the question of whether VTE prophylaxis is needed in CS patients at discharge from hospital (20).

Consensus Statement about VTE in CS

Thrombophilic state in CS is caused by hypercoagulability on the one hand and impaired fibrinolysis on the other hand. The increased cortisol levels stimulate the synthesis of clotting factors such as fibrinogen and von Willebrand factor, leading to hypercoagulability. High levels of cortisol also induce a higher concentration of plasminogen activator inhibitor type 1, which is the main inhibitor of the fibrinolytic system (25). It causes impaired fibrinolysis and worsens up hypercoagulability state. This is why all active CSs should be understood as having a prothrombic state and thromboprophylaxis ought to be considered (25).

Meta-analyses of the studies about VTE in CS

In 2009, a meta-analysis by Van Zaane *et al*. evaluated eight studies with 476 CS patients. It demonstrated that CS patients had increased risk for VTE regardless of surgical interventions, i.e. unprovoked VTE is also more prevalent in CS (26). The most recent, 2019 meta-analysis included 48 studies with 7,142 patients with endogenous CS (including Cushing's disease) undergoing transsphenoidal surgery or adrenalectomy (1). The risk of unprovoked VTE was almost 18 times higher in CS in comparison with a healthy population (1). Admittedly, patients with endogenous CS had not so high odds of VTE as compared to patients who undergo orthopedic surgery for hip repair. The same analysis confirmed that CS-associated risk of VTE is intermediate between the general population and orthopedic surgical interventions (1). Wagner *et al.* also emphasized the

fact that patients with CS have a different coagulation profile as compared to controls. Namely, CS patients have increased von Willebrand factor and factor VIII, while activated partial thromboplastin time (aPTT) is decreased (1).

CS in VTE guidelines

The evidence, including that from meta-analyses, demonstrates consistently increased risk of VTE in both endogenous and exogenous CS. Having in mind high prevalence, mortality, and morbidity in VTE, and therefore very high medical and social significance of this disease, it is logical to expect at least a mention of CS and Cushing's disease in VTE guidelines. However, having performed a search in guidelines on the topic, we discovered that none of the 27 VTE/PTE/DVT guidelines published between 2000 and 2019 contained the term "Cushing" (27-53).

DISCUSSION

The most important finding in this study is the discrepancy between numerous studies and meta-analyses suggesting that CS is a risk factor for VTE on the one hand, and the absence of such data in 27 guidelines for VTE on the other. Meta-analyses provide an excellent tool for confirming the association between the two diseases.

Pathophysiologic mechanisms

Hypercoagulability state is the main pathophysiological mechanism that is responsible for the increased risk of VTE in CS. The disturbance of hemostatic balance is caused by the overproduction of coagulation proteins on one, and impaired fibrinolysis on the other hand (20). The pathogenesis of hypercoagulability in CS is complex and multifactorial. Several studies have shown that patients with CS have increased levels of von Willebrand factor, Factor VIII, Factor IX, and fibrinogen compared to healthy controls. This is probably due to the direct stimulating effect that glucocorticoids have on clotting factor production. Shortened aPTT in these patients is caused by activation of the coagulation pathways (54). Factor VIII higher than 160% carries a 4-fold increased risk of VTE (55). On the other hand, patients with CS suffer from abdominal obesity which is associated with increased levels of Factor VII, von Willebrand factor, and PAI-1. Increased concentrations of clotting factors in these individuals are probably caused by increased abdominal fat mass. Interestingly, a hypercoagulable state in CS persists even after normalization of cortisol levels. This observation gives an advantage to abdominal obesity as a probably more important factor for thrombosis in CS compared to hypercortisolemia (56). Impaired fibrinolysis in CS is a common finding as these patients have increased levels of fibrinolysis inhibitors such as PAI-1, TAFI, 2-antiplasmin (56). Homocysteinaemia and hyperfibrinogenemia are valid predictors of VTE (5). Polycythemia also represents a thrombogenic factor as it increases blood viscosity (57). Patients with CS and VTE have higher urinary free cortisol and von Willebrand factor levels compared to CS without VTE (55). Also, patients with CS and VTE are more likely to have prothrombin gene 20210A variants. Second to that, GCAG/GCAG genotype which is known to induce hypersecretion of VWF is more common in patients with CS and VTE (55, 58). A positive association between elevated D-dimer and cortisol levels suggests that the crucial factor for thrombosis is not daily cortisol level but autonomous cortisol secretion.

The narrative review may add information on how widely this association is recognized, whether it is accepted by the medical community or not, and whether it is available in the essential documents in the field (guidelines) aimed at teaching pathophysiology and instructing in the clinical practice. For example, when we estimate the pre-test probability for VTE in an individual patient, it is helpful to be aware that CS is a risk factor (for VTE) and the guidelines are a very important source of such information.

In conclusion, it is important to recognize that glucocorticoids are per se thrombogenic. Moreover, Cushing's disease or adrenal adenoma are neoplasms (endogenous CS), and therefore prothrombotic, too. Additionally, the probability of thrombosis in iatrogenic, exogenous CS increases not only due to glucocorticoids, but also thrombogenicity stems from pronounced inflammatory pathophysiology of some diseases (such as systemic lupus erythematosus or rheumatoid arthritis, which are indications for glucocorticoids). Over the period of 50 years considerable evidence confirming the increased VTE risk in CS has been accumulated. This is true for both endogenous and exogenous type of CS and confirmed in the great majority, if not all the available studies, including meta-analyses. In sharp contrast, PTE guidelines do not even mention CS as a VTE risk factor. The more active inclusion of VTE in differential diagnostic consideration in patients with CS seems justified. It is important that, not only physicians who treat CS, but also physicians who manage patients with suspected VTE be aware of increased VTE risk.

Conflict of interest

Authors have no relevant conflict of interest to disclose.

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References

1. Wagner J, Langlois F, Lim DST, McCartney S, Fleseriu M. Hypercoagulability and Risk of Venous Thromboembolic Events in Endogenous Cushing's Syndrome: A Systematic Meta-Analysis. Front Endocrinol (Lausanne). 2019; 9:805.
2. Koracevic G, Stojkovic M, Lovic D, Pavlovic M, Kostic T, Kutlesic M, Micic S, Koracevic M, Djordjevic M. Cushing's Syndrome should be Cited as a Disease with High Cardiovascular Risk in Relevant Guidelines. Curr Vasc Pharmacol. 2020; 18(1):12-24.
3. Johannesdottir SA, Horváth-Puhó E, Dekkers OM, Cannegieter SC, JØrgensen JOL, Ehrenstein V, Vandenbroucke JP, Pedersen L, SØrensen HT. Use of glucocorticoids and risk of venous thromboembolism: a nationwide population-based case-control study. JAMA Intern Med. 2013; 173(9):743-752.
4. Giordano R, Picu A, Marinazzo E, D'Angelo V, Berardelli R, Karamouzis I, Forno D, Zinná D, Maccario M, Ghigo E, Arvat E. Metabolic and cardiovascular outcomes in patients with Cushing's syndrome of different aetiologies during active disease and 1 year after remission. Clin Endocrinol (Oxf). 2011; 75(3):354-360.
5. Miljic P, Miljic D, Cain JW, Korbonits M. Pathogenesis of vascular complications in Cushing's syndrome. Hormones. 2012; 11(1):21-30.
6. De Leo M, Pivonello R, Auriemma RS, Cozzolino A, Vitale P, Simeoli C, De Martino MC, Lombardi G, Colao A. Cardiovascular Disease in Cushing's Syndrome: Heart *versus* Vasculature. Neuroendocrinology. 2010; 92(1):50-54.
7. Pezzulich RA, Mannix JrH. Immediate complications of adrenal surgery. Ann Surg. 1970; 172:125-130.
8. Sjoberg HE, Blomback M, Granberg PO. Thromboembolic Complications, Heparin Treatment and Increase in Coagulation Factors in Cushing's Syndrome. Acta Med. Scand. 1976; 199:95.
9. Conn W. Epidemiology of Venous Thromboembolism. Ann Surg. 1977; 186:149-164.
10. Stuijver DJ, van Zaane B, Feelders RA, Debeij J, Cannegieter SC, Hermus AR, van den Berg G, Pereira AM, de Herder WW, Wagenmakers MAEM, Kerstens MN, Zelissen PMJ, Fliers E, Schaper N, Drent ML, Dekkers OM, Gerdes VEA. Incidence of venous thromboembolism in patients with Cushing's syndrome: a multicenter cohort study. J Clin Endocrinol Metab. 2011; 96(11):3525-3532.
11. Small M, Lowe GDO, Forbes CD, Thomson JA. Thromboembolic complications in Cushing's syndrome. Clinical endocrinology. 1983; 19(4):503-511.
12. Manetti L, Bogazzi F, Giovannetti C, Raffaelli V, Genovesi M, Pellegrini G, Ruocco L, Iannelli A, Martino E. Changes in coagulation indexes and occurrence of venous thromboembolism in patients with Cushing's syndrome: results from a prospective study before and after surgery. Euro J Endocrinol. 2010; 163(5):783-791.
13. Boscaro M, Sonino N, Scarda A, Barzon L, Fallo F, Sartori MT, Patrassi GM, Girolami A. Anticoagulant prophylaxis markedly reduces thromboembolic complications in Cushing's syndrome. J Clin Endocrinol Metab. 2002; 87(8):3662-3666.
14. La Brocca A, Terzolo M, Pia A, Paccotti P, De Giuli P, Angeli A. Recurrent thromboembolism as a hallmark of Cushing's syndrome. J Endocrinol Invest. 1997; 20(4):211-214.
15. Diez JJ, Iglesias P. Pulmonary thromboembolism after inferior petrosal sinus sampling in Cushing's syndrome. Clin Endocrinol (Oxf). 1997; 46(6):777.
16. Obuobie K, Davies JS, Ogunko A, Scanlon MF. Venous thrombo-embolism following inferior petrosal sinus sampling in Cushing's disease. J Endocrinol Invest. 2000; 23(8):542-544.
17. Zilio M, Mazzai L, Sartori MT, Barbot M, Ceccato F, Daidone V, Casonato A, Saggiorato G, Noventa F, Trementino L, Prandoni P, Boscaro M, Arnaldi G, Scaroni C. A venous thromboembolism risk assessment model for patients with Cushing's syndrome. Endocrine. 2016; 52(2):322-332.
18. Dekkers OM, Horváth-Puhó E, Jørgensen JO, Cannegieter SC, Ehrenstein V, Vandenbroucke JP, Pereira AM, Sørensen HT. Multisystem morbidity and mortality in Cushing's syndrome: a cohort study. J Clin Endocrinol Metab. 2013; 98(6):2277-2284.
19. Huerta C, Johansson S, Wallander MA, Rodriguez LAG. Risk factors and short-term mortality of venous thromboembolism diagnosed in the primary care setting in the United Kingdom. Arch Intern Med. 2007; 167(9):935-943.
20. Babic B, De Roulet A, Volpe A, Nilubol N. Is VTE Prophylaxis Necessary on Discharge for Patients Undergoing Adrenalectomy for Cushing Syndrome? J Endocr Soc. 2018; 3(2):304-313.
21. Jacoby RC, Owings JT, Ortega T, Gosselin R, Feldman EC. Biochemical basis for the hypercoagulable state seen in Cushing syndrome; discussion 1006-7. Arch Surg. 2001; 136(9):1003-1006.
22. Etxabe J, Vazquez JA. Morbidity and mortality in Cushing's disease: an epidemiological approach. Clin Endocrinol (Oxf). 1994; 40(4):479-484.
23. Yale SH, Medlin SC, Liang H, Peters T, Glurich I, Mazza JJ. Risk assessment model for venothromboembolism in post-hospitalized patients. Int Angiol. 2005; 24(3):250-254.
24. Russell MW, Taylor DC, Cummins G, Huse DM. Use of managed care claims data in the risk assessment of venous thromboembolism in outpatients. Am J Manag Care. 2002; 8(1):S3-S9.
25. Arnaldi G, Angeli A, Atkinson AB, Bertagna X, Cavagnini F, Chrousos GP, Fava GA, Findling JW, Gaillard RC, Grossman AB, Kola B, Lacroix A, Mancini T, Mantero F, Newell-Price J, Nieman LK, Sonino N, Vance ML, Giustina A, Boscaro M. Diagnosis and complications of Cushing's syndrome: a consensus statement. J Clin Endocrinol Metab. 2003; 88(12):5593-5602.
26. Van Zaane B, Nur E, Squizzato A, Dekkers OM, Twickler MTB, Fliers E, Gerdes VEA, Buller HR, Brandjes DPM. Hypercoagulable state in Cushing's syndrome: a systematic review. J Clin Endocrinol Metab. 2009; 94(8):2743-2750.
27. Guidelines on diagnosis and management of acute pulmonary embolism. Task Force on Pulmonary Embolism, European Society of Cardiology. Eur Heart J. 2000; 21(16):1301-1336.
28. British Thoracic Society Standards of Care Committee Pulmonary Embolism Guideline Development Group. British Thoracic Society guidelines for the management of suspected acute pulmonary embolism. Thorax. 2003; 58(6):470-483.
29. Hill J, Treasure T. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients having surgery: summary of NICE guidance. BMJ. 2007; 334(7602):1053-1054.
30. Snow V, Qaseem A, Barry P, Hornbake ER, Rodnick JE, Tobolic T, Ireland B, Segal JB, Bass EB, Weiss KB, Green L, Owens DK. Joint American College Of Physicians/American Academy of Family Physicians Panel On Deep Venous Thrombosis/pulmonary Embolism. Management of venous thromboembolism: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Ann Fam Med. 2007; 5(1):74-80.
31. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR,Colwell CW. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008; 133(6):381S-453S.
32. Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galie

N, Pruszczyk P, Bengel F, Brady AJB, Ferreira D, Janssens U, Klepetko W, Mayer E, Remy-Jardin M, Bassand JP. Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology. Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J. 2008; 29(18):2276-2315.
33. JCS Joint Working Group. Guidelines for the diagnosis, treatment and prevention of pulmonary thromboembolism and deep vein thrombosis (JCS 2009). Circ J. 2011; 75(5):1258-1281.
34. Hill J, Treasure T; Guideline Development Group. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital: summary of the NICE guideline. Heart. 2010; 96(11):879-882.
35. Mandalà M, Falanga A, Roila F. ESMO Guidelines Working Group. Venous thromboembolism in cancer patients: ESMO Clinical Practice Guidelines for the management. Ann Oncol. 2010; 21(5):274-276.
36. Qaseem A, Chou R, Humphrey LL, Starkey M, Shekelle P. Clinical Guidelines Committee of the American College of Physicians. Venous thromboembolism prophylaxis in hospitalized patients: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2011; 155(9):625-632.
37. Mandalà M, Falanga A, Roila F; ESMO Guidelines Working Group. Management of venous thromboembolism (VTE) in cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol. 2011; 22(6):85-92.
38. Jaff MR, McMurtry MS, Archer SL, Cushman M, Goldenberg N, Goldhaber SZ, Jenkins JS, Kline JA, Michaels AD, Thistlethwaite p, Vedantham S, White RJ, Zierler BK. American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; American Heart Association Council on Peripheral Vascular Disease; American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation. 2011; 123(16):1788-1830.
39. Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, Samama CM. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141(2):227S-277S. Erratum in: Chest. 2012; 141(5):1369.
40. National Institute for Health and Clinical Excellence. Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing. CG144. 2012. Downloaded from http://www.nice.org.uk/guidance/cg144 on 10/15/2014.
41. Cardiovascular Disease Educational and Research Trust; European Venous Forum; North American Thrombosis Forum; International Union of Angiology; Union Internationale du Phlebologie. Prevention and treatment of venous thromboembolism: international consensus statement (guidelines according to scientific evidence). Clin Appl Thromb Hemost. 2013; 19(2):116-118.
42. Uresandi F, Monreal M, García-Bragado F, Domenech P, Lecumberri R, Escribano P, Zamorano JL, Jimenez S, Ruiz-Artacho P, Lozano F, Romera A, Jimenez D, Bellmunt S, Cuenca J, Fernandez A, Fernandez F, Ibanez V, March JR, Almenar L, Castro A, Lazaro M, Alonso JR, Casal JR, Franco JM, Merlo M, Perales R, Pinera P, Suero C, Barba R, Fernandez-Capitan C, Garcia-Bragado F, Gomez V, Nieto JA, Riera-Mestre A, Suarez C, Trujillo-Santos J, Congest F, Jara L, Jimenez D, Lobo JL, de Miguel J, Nauffal D, Oribe M, Otero R, Gonzales-Porras JR, Llamas P, Mingot E, Pina E, Rodriguez-Martorell J. National consensus on diagnosis, risk stratification and treatment of patients with pulmonary thromboembolism. Arch Bronconeumol. 2013; 49(12):534-547.
43. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galie N, Gibbs JSR, Huisman MV, Humbert M, Kucher N, Lang I, Lankeit M, Lekakis J, Maack C, Mayer E, Meneveau N, Perrier A, Pruszczyk P, Rasmussen LH, Schindler TH, Svitil P, Noordegraaf AV, Zamorano JL, Zompatori M. Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2014; 35(43):3033-3069
44. Kuderer NM, Lyman GH. Guidelines for treatment and prevention of venous thromboembolism among patients with cancer. Thromb Res. 2014; 133(2):S122-S127.
45. Watson HG, Keeling DM, Laffan M, Tait RC, Makris M. British Committee for Standards in Haematology. Guideline on aspects of cancer-related venous thrombosis. Br J Haematol. 2015; 170(5):640-648.
46. Raja AS, Greenberg JO, Qaseem A, Denberg TD, Fitterman N, Schuur JD. Clinical Guidelines Committee of the American College of Physicians. Evaluation of Patients With Suspected Acute Pulmonary Embolism: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians. Ann Intern Med. 2015; 163(9):701-711.
47. Khorana AA, Carrier M, Garcia DA, Lee AYY. Guidance for the prevention and treatment of cancer-associated venous thromboembolism. J Thromb Thrombolysis. 2016; 41(1):81-91.
48. Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. J Thromb Thrombolysis. 2016; 41(1):3-14.
49. Pulmonary Embolism (PE): Treatment 2016 Thrombosis Canada. Downloaded from: http://thrombosiscanada.ca/wp-content/uploads/2017/01/5.-Pulmonary-Embolism-Treatment-2016Dec07-FINAL-1.pdf
50. Min SK, Kim YH, Joh JH, Kang JM, Park UJ, Kim HK, Chang JH, Park SJ, Kim JY, Bae JI, Choi SY, Kim CW, Park SI, Yim NY, Jeon YS, Yoon HK, Park KH. Diagnosis and Treatment of Lower Extremity Deep Vein Thrombosis: Korean Practice Guidelines. Vasc Specialist Int. 2016; 32(3):77-104.
51. Mazzolai L, Aboyans V, Ageno W, Agnelli G, Alatri A, Bauersachs R, Brekelmans MPA, Buller HB, Elias A, Farge D, Konstantinides S, Palareti G, Prandoni P, Righini M, Torbicki A, Vlachopoulos C, Brodmann M. Diagnosis and management of acute deep vein thrombosis: a joint consensus document from the European society of cardiology working groups of aorta and peripheral circulation and pulmonary circulation and right ventricular function. Eur Heart J. 2018; 39(47):4208-4218.
52. National Institute For Health and Care Excellence. Venous thromboembolic diseases: 4 diagnosis, management and thrombophilia testing (update). Downloaded from: https://www.nice.org.uk/guidance/cg144.
53. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, Huisman MV, Humbert M, Jennings CS, Jimenez D, Kucher N, Lang IM, Lankeit M, Lorusso R, Mazzolai L, Meneveau N, Ni Ainle F, Prandoni P, Pruszczyk P, Righini M, Torbicki A, Van Belle E, Zamorano JL. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Heart J. 2019; 00:1-61.
54. Targher G, Zoppini G, Moghetti P. Day CP. Disorders of coagulation and hemostasis in abdominal obesity: emerging role of fatty liver. Semin Thromb Hemost. 2010; 36:41–48.
55. Koutroumpi S, Daidone V, Sartori MT, Gattini MG, Albiger NM, Occhi G, Ferasin S, Frigo A, Mantero F, Casonato A, Scaroni C. Venous thromboembolism in patients with Cushing's syndrome: need of a careful investigation of the prothrombotic risk profile. Pituitary. 2013; 16(2):175-181.

56. van der Pas R, de Bruin C, Leebeek FW, de Maat MPM, Rijken DC, Pereira AM, Romijin JA, Netea-Maier RT, Hermus AR, Zelissen PMJ, de Jong FH, van der Lely AJ, de Herder WW, Lamberts SWJ, Hofland LJ, Feelders RA. The hypercoagulable state in Cushing's disease is associated with increased levels of procoagulant factors and impaired fibrinolysis, but is not reversible after short-term biochemical remission induced by medical therapy. J Clin Endocrinol Metab. 2012; 97(4):1303-1310.

57. Giri S, Mehta KD, Bhatt VB. Secondary Polycythemia and the Risk of Venous Thromboembolism (VTE) Among Hospitalized Patients in the United States. Blood. 2016; 128:1427

58. Fukuoka H, Takeuchi T, Matsumoto R, Bando H, Suda K, Nishizawa H, Takahashi M, Hirota Y, Iguchi G, Takahashi Y. D-dimer as a significant marker of deep vein thrombosis in patients with subclinical or overt Cushing's syndrome. Endocr J. 2014; 61(10):1003-1010.