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COVID and venous thrombosis: systematic review of literature.

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ABSTRACT

INTRODUCTION: We aimed to review the prevalence, the risk factors and the outcomes of venous thrombosis (VT) in patients hospitalized for COronaVirus Disease 19 (COVID-19).

METHODS: Electronic bibliographic databases were searched using the words “COVID venous thrombosis”. The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement standards.

RESULTS: The search of the Literature retrieved 877 results. After assessment of full texts, 69 papers were included in the qualitative analysis and 23 of them in the quantitative evaluation. The analyzed

studies included a total of 106838 patients hospitalized for COVID-19 from 01/2020 to 12/2020. The pooled reported prevalence rate of VT was in median 16.7% (IQR 5.8%-30%), being higher in ICU patients (60.8%-85.4%). VT events were reported in about 75% of cases in the popliteal and calf veins. Signs and symptoms were present in 6.1% of cases. At quantitative evaluation, older age, D-dimer and obesity increased the odds to experience a VT (OR 3.54, 95%CI 0.65-6.43, P=0.01; OR=956.86, 95%CI 225.67-1668.05, P=0.01; OR 1.42, 95%CI 1.01-1.99, P=0.03 respectively). Female sex seemed to be protective against the odds of VT (OR 0.77, 95%CI 0.63-0.93, P=0.007).

CONCLUSION: Among patients hospitalized for COVID-19, VT is a relatively common finding, with higher prevalence rates in ICU patients. VT occurs mostly in the distal regions of the lower limb and is asymptomatic in most cases. Older age, obesity and higher D-dimer values on admission increased the odds of VT, while female sex was protective against the odds of VT.

Key-words: COVID-19, venous thrombosis, SARS-CoV-2

MANUSCRIPT

INTRODUCTION

COronariVIrus Disease 19 (COVID-19) may be responsible for a wide spectrum of clinical illnesses, ranging from asymptomatic cases to mild disease, up to interstitial pneumonia that can rapidly evolve to acute respiratory distress syndrome (ARDS) in most severe cases [1].

Moreover, the strong virus affinity for vessel layers, besides the intense systemic inflammatory response, can cause activation of the coagulation cascade and lead to vascular thrombosis, with different clinical pictures depending on the affected system [2]. These thrombotic complications may suddenly precipitate the patient's prognosis and therefore require prompt diagnosis and treatment.

In particular, venous thromboembolism has been associated with increased mortality and morbidity rates [3]. Nevertheless, the accurate estimation of venous thrombosis (VT) incidence in patients hospitalized for COVID-19 is still unclear.

Aim of this work was to systematically review the literature about the prevalence, the risk factors and the outcomes of VT in patients hospitalized for COVID-19.

MATERIALS AND METHODS

This systematic review was written in accordance with the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) statement [4] and following PICO model. For this review registration was requested to the international prospective register of systematic reviews (PROSPERO).

Search strategy

A literature search was conducted on PubMed and Embase using the words "COVID venous thrombosis" on 31st May, 2021. All search results were restricted to English, Italian and French language.

Study selection

Two researchers independently screened records for inclusion and were blinded to each other's' decisions. Disagreements between individual judgements were resolved by a third independent reviewer. Studies included randomized controlled trials, cohort studies and case series of patients affected by venous thrombotic events in COVID-19. Reviews without any available data, conference proceedings, letters without any available data, case reports, papers reporting about thrombosis after COVID-vaccine or cerebral venous thrombosis, studies describing necroscopy results, papers whose results were partially or totally included in other publications and papers whose full-text was not available were excluded.

From study documents, data were extracted about study design and methodology. We collected data about the prevalence of VT and its localization, the pathophysiology and risk factors, the clinical presentation, the diagnosis, the treatment and the outcomes.

Two researchers independently extracted the data, with a third reviewer who acted as judge in case of any disagreement.

Quality assessment was done at study level by two reviewers, according to the Oxford Centre for Evidence-Based Medicine (CEBM) Levels of Evidence (March 2009) [5].

Studies which reported concomitant data about a comparison group of patients hospitalized for COVID-19 and without VT were included in the quantitative analysis.

Statistical Analysis

The qualitative data are presented in a descriptive manner, therefore proportion, percentages, median and inter-quartile range (IQR) are reported.

For the quantitative data, package "meta" R program (http://CRAN.R-project.org) was used to explore the association of VT in COVID-19 patients (i.e. presence/absence) with presence or absence of comorbidities using odds ratios (ORs). Continuous outcome data were expressed with mean difference (MD) and corresponding 95% confidence intervals (CIs).

The heterogeneity of the included studies was evaluated by the χ^2 test on Cochrane's Q statistic and quantified by the I^2 statistic. I^2 values of 25%, 50% and 75% were considered as representing low, medium and high heterogeneity respectively.

The choice between the fixed-effects and the random-effects model was performed based on the evidence of statistical heterogeneity among the studies. The combined ORs or MD and the corresponding 95% CIs were calculated and reported in the Forest plot. The risk of potential publication bias was evaluated by linear regression test of funnel plot asymmetry (efficient score). Two-sided P-values less than 0.05 were considered statistically significant.

RESULTS

The search of the Literature retrieved 877 results (Figure 1). Of them, 785 were excluded from the title or after the reading of the abstract. After assessment of full texts, a total of 69 papers were then included in the qualitative analysis and 23 of them in the quantitative evaluation.

At quality assessment, all studies were classified to have a 2b level of evidence, since they all were retrospective or cross-sectional cohort studies from either single or multiple institutions.

The analyzed studies included a total of 106838 patients hospitalized for mild to severe COVID-19 pneumonia during the first and second wave of the pandemic (from January 2020 to December 2020). Of them, 2686 were critically ill patients at the time of VT diagnosis and therefore were already in intensive care unit (ICU).

Prevalence and localization of venous thrombosis

The reported prevalence of VT was highly variable and subject to many selection biases, such as differences in study design that included or not a systematic screening for VT, the method of diagnosis, or the type of the analyzed cohort of patients. Particularly, VT was overrepresented in critically-ill COVID-19 patients, with a reported prevalence ranging from 60.8% [6] to 85.4% [7] of ICU patients (Table I), which was higher than that reported in non-COVID-19 ICU patients [8].

In non-ICU COVID-19 patients, the reported rates of VT ranged from 3% [9] to 47.9% [3]. Studies of non-ICU cohorts which included a systematic screening for VT using Duplex UltraSound (DUS) reported a prevalence of VT which was also variable, ranging from 10.5% to 47.9% but being more frequently around 20% [3, 11, 14, 28, 32, 34, 35, 37 56, 58, 59, 64, 67, 71] (Table I). These rates were comparable to those reported in studies in which DUS was performed only when symptoms or laboratory values raised the suspicion of VT [18].

Overall, the pooled reported prevalence rate was in median 16.7% (IQR 5.8%-30%).

VT events were reported both in the deep and in the superficial venous system, being in about three quarter of the cases in the popliteal and calf veins. In fact, VT was more frequently detected in the lower extremities, but also upper extremities and jugular veins were affected, especially when the VT was line-related. Less frequently, the portal vein [10, 40, 43, 47] and the inferior vena cava [47] were reported to be site of VT.

Pathophysiology and risk factors

The pathophysiology of VT events is complex and somewhat different from that reported in other infectious diseases [12]. Abnormal coagulation parameters are frequently described in patients affected by COVID-19, and present unique features. At initial phases of the diseases, laboratory values show minimal abnormalities in prothrombin time and platelet count, while increased D-dimer and fibrinogen levels are typical of the advanced stages of the disease, being associated with clinical worsening and with enhanced mortality, especially in ICU patients [74].

The raise of these coagulation products in the peripheral blood is a consequence of a complex mechanism in which the infection triggers a proinflammatory responses and activates the systemic coagulation. From one side, the release of proinflammatory cytokines such as interleukin (IL)-1β, IL-6 and tumor necrosis factor-α (TNFα) as host defense for the ultimate killing of the pathogen, can induce both coagulopathy and endothelial damage that further increases thrombin generation [75].

On the other side, the SARS-CoV-2 itself may directly invade and disrupt the endothelial cells through the angiotensin converting enzyme 2 receptor [76].

Additionally, it is still unclear whether antiphospholipid antibodies or lupus anticoagulant may play a role in the pathogenesis of thrombosis in patients with COVID-19 pneumonia [72]. As for Virchow's triad, VT events are finally the results of the interplay between the hypercoagulability status, the endothelial injury and the stasis of the blood flow which can be a consequence of the prolonged bed rest, especially in more critically ill patients.

In their univariate analysis of the data of 143 COVID-19 patients (23 of them in ICU), Zhang et al. [73] reported that age >65, the bedridden time, the Padua prediction score, the Wells score, the disease severity status and the pro-coagulant and inflammatory status at laboratory values (leukocytosis; neutrophilia; lymphocyte count; prothrombin time; elevated serum D-dimer, C-reactive protein, procalcitonin, blood urea nitrogen, and lactic dehydrogenase) were associated with increased odds of VT. At multivariable analysis, the Padua prediction score and the D-dimer levels at admission confirmed to be risk factors for the occurrence of VT events.

Similarly, Cai et al [3] identified older age (OR, 1.05; 95% CI, 1.00-1.10; p=0.0306), female sex (OR, 3.39; 95% CI, 0.99-11.63; p=0.0521), higher C-reactive protein (CRP) level (OR, 1.02; 95% CI, 1.01-1.04; p=0.0040), and higher D-dimer levels on admission (OR, 1.42; 95% CI, 1.15-1.76; p=0.0010) to be risk factors for VT among COVID-19 patients at multivariable analysis.

Surprisingly, the presence of an active cancer did not seem to have impact on the occurrence of VT, as described by Patell et al. [61], who reported a cumulative incidence of thrombosis of 18.2% in the non-cancer and 14.2% cancer cohorts of COVID-19 patients. Nevertheless, there are still limited data about this subgroup of patients.

According to our quantitative evaluation, the presence of active cancer did not seem to increase the odds of VT (OR 1.10, 95%CI 0.79-1.52, P=0.55, Table II). On the other side, older patients had higher odds to experience a VT (OR 3.54, 95%CI 0.65-6.43, P=0.01), Figure 2A, while female sex seemed to be protective against the odds of VT (OR 0.77, 95%CI 0.63-0.93, P=0.007), Figure 3A. As showed

in Table II, obesity was found to increase the odds of VT of 1.4 times (OR 1.42, 95%CI 1.01-1.99, P=0.03), Figure 3B. Also higher D-dimer values on admission were correlated to higher odds of VT (OR=956.86, 95%CI 225.67-1668.05, P=0.01), Figure 2B.

Clinical presentation

Most VT events occurred asymptomatically even with adequate thromboprophylaxis, and this was especially described in ICU patients [54, 58]. Symptoms and signs of VT were reported only in 6.1% of cases of VT, being typically pain and/or leg swelling.

In most cases the evidence of VT was accompanied by a raise of the CRP, and particularly of the D-dimer values, these latter in most cases were at least three times higher than the normal reference values [3, 38, 45, 53, 57, 66, 73].

Diagnosis

Most VTs were found using DUS. The utility of a bedside DUS examination for a prompt diagnosis of VT was highlighted by Alfageme et al. [6], who described DUS as a "game-changer" that helped in the decision to switch from a simple thromboprophylaxis towards a full anticoagulant therapy, especially for ICU patients.

In all studies that specifically aimed at the detection of VT, DUS was systematically performed by skilled and experienced operators [32]. Nevertheless, a complete DUS can be time-consuming and during the COVID-19 pandemic may expose the operators to a higher risk of infection. Furthermore, Lapebie et al. [77] in their prospective study of consecutive patients admitted in three ICUs for COVID-19 pneumonia, observed that systematic screening for VT in patients hospitalized in ICU was not associated with a higher diagnosis of VT events or a reduced diagnosis of pulmonary embolism.

As a faster but feasible alternative to DUS, two-region compression ultrasound (2-CUS) of the common femoral and popliteal veins only, has been reported to be accurate for diagnosing VT in

critically ill COVID-19 patients, and can be performed in an emergent and critical care setting even by residents with limited experience in DUS [13].

VTs were also detected at contrast-enhanced CT (CE-CT), especially when the thrombosis was in the splanchnic district or in the inferior vena cava. However, CE-CT was not performed as a first-line examination for VT but often to rule out the suspicion of pulmonary embolism, with a contextual occasional finding of VT [39].

Besides the presence of symptoms and signs of TV, a sudden raise of the D-dimer values was often the indication for the search of a possible site of thrombosis.

Different values of D-dimer have been proposed as possible cut-off for the suspicion of VT. Baccellieri et al. found that D-dimer values >5000 ng/mL were prognostic for VT at their multivariable analysis [38]. Gibson et al. [53] in ICU setting observed a good reliability at or above a concentration of 3000 ng/mL. Pizzolo et al. [45], proposed even a lower threshold, above 1500 ng/mL. However, D-dimer levels are typically elevated in patients with COVID-19 even without TV, therefore the sensitivity of the test could be distorted. Cho et al. [60] observed that a D-dimer level of less than 6494 ng/mL could exclude VT, limiting the need for DUS examinations [60].

Adjunctive tools such as tromboelastography have not proved useful in the risk stratification for the development of VT or in the decision-making process about anticoagulation [23].

Treatment and outcomes

The current Literature lacks evidence regarding anticoagulation strategies for COVID-19 patients with VT. Nevertheless, CHEST guidelines recommend anticoagulation therapy for a minimum of three months after VT events, with therapeutic weight-adjusted low-molecular-weight heparin (LMWH) or parenteral unfractionated heparin as the initial drug of choice [78].

On the other side, the importance of thromboprophylaxis is universally accepted in COVID-19 patients, since it has shown to reduce mortality in severely ill patients [79], but evidence comes after

the observations from cohort studies and strong evidence from properly designed clinical trials is missing.

Current regimen of thromboprophylaxis on admission recommend an individualized patient-based approach which could take into consideration the underlying risk of having a thrombotic event. A position paper from the Italian Society on Thrombosis and Haemostasis recommends the administration of thromboprophylaxis for the entire duration of the hospital stay and for 7-14 days after hospital discharge, especially in presence of risk factors such as reduced mobility, obesity, active cancer or history of previous VT. In particular, the use of intermediate-dose LMWH (i.e., enoxaparin 4000 IU subcutaneously every 12 hours) is suggested in patients deemed to be at high risk for thrombotic events [80].

Actual guidelines also recommend against increased doses of heparin [78, 80]. Chronic kidney disease, the occurrence of acute kidney injury or hepatic injury are common findings in seriously ill COVID-19 patients and may increase the activity of anticoagulant drugs. Major bleeding events have in fact been reported, especially in patients with high dosages of anticoagulation for either prophylaxis or treatment of VT. The rates of occurrence of bleeding complications ranged from 0.9% [14] to 5% [36] in the overall cohort of hospitalized patients (Table I), requiring surgical treatment and blood transfusions in most cases.

Enoxaparin is largely employed for thromboprophylaxis in hospitalized COVID-19 patients, while Russo et al. [36] in their study provided preliminary evidence of a safe and efficacy use of fondaparinux as a valid alternative.

As a matter of fact, VT events may happen even in anticoagulated patients [14, 18, 19].

The occurrence of VT has been sometimes associated to increased mortality [3], most in ICU patients [66], but it is still unclear whether VT can be considered an independent predictor of death itself or may only reflect the severity of the disease. Reported mortality rates of COVID-19 patients with VT ranged from 5% [30] to 33.3% [54] in ICU settings, and from 0% [11] to 27.5% [3] in the cohort of non-ICU patients (Table I), but it did not differ significantly from that of non-VT patients [38, 66].

Concomitant pulmonary embolism (PE) has been reported with extremely variable rates (Table I). According to the pooled analysis, the rate of PE was however 6.5%.

DISCUSSION

Among patients hospitalized for COVID-19, VT is a relatively common finding [3], secondary to the combination of known thrombotic risk factors (inflammation, hypoxia and immobilization) with viral-induced hypercoagulability. Overall, there is a higher prevalence of VT events in ICU patients if compared to those hospitalized in non-ICU wards.

Nevertheless, the real prevalence of VT on COVID-19 patients may be underestimated because of the cross-sectional or retrospective design of the studies reporting data about this issue, and because in most cases there was no systematic exploration of distal venous axis, which is the most affected localization.

In addition, most VTs occur asymptomatically, which may also lower the number of recorded events.

The detection of VT is usually made using DUS. As a matter of fact, a 2-point CUS can be a feasible alternative to complete DUS [13], with a reduction of time for the execution and a consequent reduction of the operator's exposure to infectious risk. Nevertheless, it should be performed bearing in mind that most VT occur in the calf region, but neck, upper extremities and splanchnic vessels may be affected too.

It has been showed that routinely screening with DUS does not reduce the incidence of VT [77], therefore results coming from the different studies suggest that a complete DUS should be performed in case of symptoms or when a raise of the D-dimer is noticed, particularly in ICU patients. D-dimer values lower than 1500 ng/mL could reasonably exclude VT [45], while a raise of the D-dimer with values above than 5000 ng/mL poses a significant suspicion for a VT event [38].

Indeed, according to our quantitative evaluation, higher D-dimer values on admission were correlated to higher odds of VT. Also older age and obesity increased the odds to experience a VT, while female sex seemed to be protective against the odds of VT.

Given the results of this review, two main issues need further clarification that will probably come by future incoming studies: the first issue regards thromboprophylaxis, and the second is about the possible correlation between VT events and the outcomes of COVID-19 patients.

Thromboprophylaxis with LMWH is highly recommended to reduce the risk of VT, but actually however there is no evidence of benefit in terms of reduced mortality or VT events when anticoagulation is performed at therapeutic-dose.

As for the second issue, COVID-19 patients with VT events carry higher risks of ICU admission and hospital stay [17]. Whether these patients have also higher mortality risks is still unclear, since in most cases outcomes and follow-up are missing. Furthermore, a control group of non COVID-19 patients with VT was lacking in most cases.

Besides these limitations, another criticism is that some data of the published studies are heterogeneous or missing. Data coming from randomized studies are therefore needed to further increase evidence about the proper prevention and treatment strategies of VT in COVID-19 patients.

CONCLUSION

Among patients hospitalized for COVID-19, VT is a relatively common finding, with higher prevalence rates in ICU patients. VT occurs mostly in the distal regions of the lower limb and is asymptomatic in most cases. Older age, obesity and higher D-dimer values on admission increased the odds of VT, while female sex seemed to be protective against the odds of VT. DUS is the method of choice for the diagnosis of VT. Thromboprophylaxis is strongly recommended to prevent VT, nevertheless a full-dose anticoagulation therapy in patients without VT is not beneficial and is discouraged given the risk of bleeding events.

CONFLICT OF INTEREST

The Authors disclose any conflict of interest.

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AUTHORS' CONTRIBUTION:

DM=Study design, literature search, data collection, data analysis, manuscript writing, critical revision, final approval

MG= literature search, critical revision, final approval

FF= literature search, critical revision, final approval

VM=data analysis, manuscript writing, critical revision, final approval

AM= critical revision, final approval

GM= critical revision, final approval

PR= critical revision, final approval

MMT= critical revision, final approval

GN= critical revision, final approval

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TABLES' AND FIGURES' LEGEND

Figure 1. Flow diagram of the results from the literature search and of the studies included in the review, according to the PRISMA statement.

Figure 2. Forest plot of the combined mean difference and the corresponding 95% confidence intervals for age (A) and D-dimer (B).

Figure 3. Forest plot of the combined odds ratios and the corresponding 95% confidence intervals for female sex (A) obesity (B).

Table I. Main features of the studies included in the qualitative review. In particular, total number of patients with incidence of venous thrombosis are reported, along with the percentages of occurrence of pulmonary embolism and death in patients with venous thrombosis. In the last column, the incidence of bleeding events in all the patients of the included cohorts was reported.

Table II. Fixed effect and random effect models of the variables analyzed in the studies included at quantitative evaluation. The chosen model is represented in bold for each variable. In the last column, the P value indicates the linear regression test of funnel plot asymmetry (efficient score).

TABLES

Table I. Main features of the studies included in the qualitative review. In particular, total number of patients with incidence of venous thrombosis are reported, along with the percentages of occurrence of pulmonary embolism and death in patients with venous thrombosis. In the last column, the incidence of bleeding events in all the patients of the included cohorts was reported.

AUTHOR	N. of patients	%VT	N. of ICU patients	% PE	mortality rates of VT patients	DUS in all patients of the cohort	% bleeding events
Cai[3]	121	47,9%	0	nr	27,6%	y	nr
Alfageme[6]	23	60,9%	23	42,9%	nr	y	13,0%
Ren[7]	48	85,4%	48	nr	31,7%	y	nr
Pellegrini[8]	57	36,8%	57	nr	nr	y	nr
Pancani[9]	66	3,0%	0	0,0%	0,0%	y	nr
Purroy[10]	1737	2,9%	117	nr	nr	n	nr
De Giorgi[11]	49	20,4%	0	nr	0,0%	y	nr
Oliva[12]	81	7,4%	nr	nr	nr	n	nr
Galien[13]	56	5,4%	56	100,0%	nr	n	nr
Pieralli[14]	227	13,7%	0	29,0%	nr	y	nr
Wu[15]	61	8,2%	1	100,0%	nr	y	nr
Mumoli[16]	476	17,2%	nr	14,6%	nr	n	nr
Jiménez[17]	74814	0,1%	nr	nr	nr	n	nr
Paredes-Ruiz[18]	58	5,2%	0	0,0%	nr	n	0,0%
Reichert[19]	107	14,0%	24	13,3%	nr	y	nr
Wang[20]	88	21,6%	31	5,3%	26,3%	n	nr
Erben[21]	915	4,9%	48	nr	nr	n	nr
Kirshblum[22]	113	22,1%	0	nr	nr	y	nr
Marvi[23]	40	17,5%	40	28,6%	nr	n	nr
Wen Tan[24]	108	2,8%	108	33,3%	nr	n	nr
Horiuchi[25]	5807	0,7%	nr	nr	nr	n	nr

Giannis[26]	10871	0,2%	nr	nr	nr	n	nr
Fujiwara[27]	628	3,0%	35	31,6%	nr	n	0,0%
Greco[28]	51	21,6%	0	nr	nr	y	nr
Bellmunt-Montoya[29]	230	23,0%	230	9,4%	nr	y	3,0%
Gonzalez-Fajardo[30]	261	7,7%	261	35,0%	5,0%	n	0,0%
Mirsadraee[31]	72	20,8%	72	nr	nr	n	nr
Ierardi[32]	263	25,5%	0	nr	nr	y	nr
Lee[33]	134	25,4%	nr	nr	nr	n	nr
Kerbikov[34]	75	20,0%	0	nr	nr	y	nr
Salisbury[35]	303	2,6%	54	37,5%	nr	n	4,3%
Russo[36]	120	5,8%	nr	nr	nr	n	5,0%
Hamadé[37]	72	16,7%	0	16,7%	nr	y	nr
Baccellieri[38]	200	14,5%	40	34,5%	17,2%	n	nr
Meiler[39]	50	4,0%	nr	nr	nr	n	nr
Kampouri[40]	443	3,2%	nr	7,1%	nr	n	nr
Motaganahalli[41]	71	47,9%	nr	nr	nr	n	nr
Thondapu[42]	138	27,5%	95	2,6%	nr	n	nr
Melazzini[43]	259	8,5%	54	nr	nr	n	nr
Hill[44]	2748	1,5%	45	nr	nr	n	nr
Pizzolo[45]	43	27,9%	0	25,0%	8,3%	y	nr
Chang[46]	188	30,9%	98	nr	19,0%	n	nr
Kapoor[47]	107	30,8%	nr	nr	nr	y	nr
Franco-Moreno[48]	26	7,7%	0	100,0%	nr	n	nr
Avruscio[49]	85	58,8%	41	nr	nr	y	nr
Rali[50]	147	9,5%	nr	35,7%	nr	y	nr
Choi[51]	1739	5,5%	68	nr	nr	n	nr
Shah[52]	187	11,8%	187	nr	nr	n	nr
Gibson[53]	72	16,7%	72	nr	8,3%	n	nr
Torres-Machorro[54]	30	30,0%	30	nr	33,3%	y	0,0%
Zermatten[55]	100	7,0%	100	nr	nr	n	nr

Jimenez-Guiu[56]	57	10,5%	0	nr	0,0%	y	nr
Yu[57]	142	35,2%	83	nr	54,0%	y	nr
Giorgi-Pierfranceschi[58]	66	13,6%	0	55,6%	nr	y	nr
Le Jeune[59]	42	19,0%	0	12,5%	25,0%	y	nr
Cho[60]	158	32,9%	92	nr	nr	y	nr
Patell[61]	398	2,5%	nr	nr	nr	n	nr
Longchamp[62]	25	24,0%	25	50,0%	nr	y	nr
Marone[63]	101	48,5%	11	22,4%	nr	y	nr
Santoliquido[64]	84	11,9%	0	nr	nr	y	nr
Trigonis[65]	45	42,2%	45	nr	nr	y	nr
Chen[66]	88	45,5%	88	nr	30,0%	y	2,3%
Koleilat[67]	135	13,3%	0	16,7%	11,1%	y	nr
Al-Samkari[68]	400	3,0%	144	25,0%	0,0%	n	nr
Voicu[69]	56	46,4%	56	nr	nr	y	nr
Nahum[70]	34	79,4%	84	nr	nr	y	nr
Artifoni[71]	75	20,0%	0	13,3%	nr	y	nr
Galeano-Valle[72]	24	54,2%	0	30,8%	nr	n	nr
Zhang[73]	143	46,2%	23	nr	34,8%	y	nr

VT=Venous Thrombosis; nr=not reported; ICU=Intensive Care Unit; PE=pulmonary embolism;

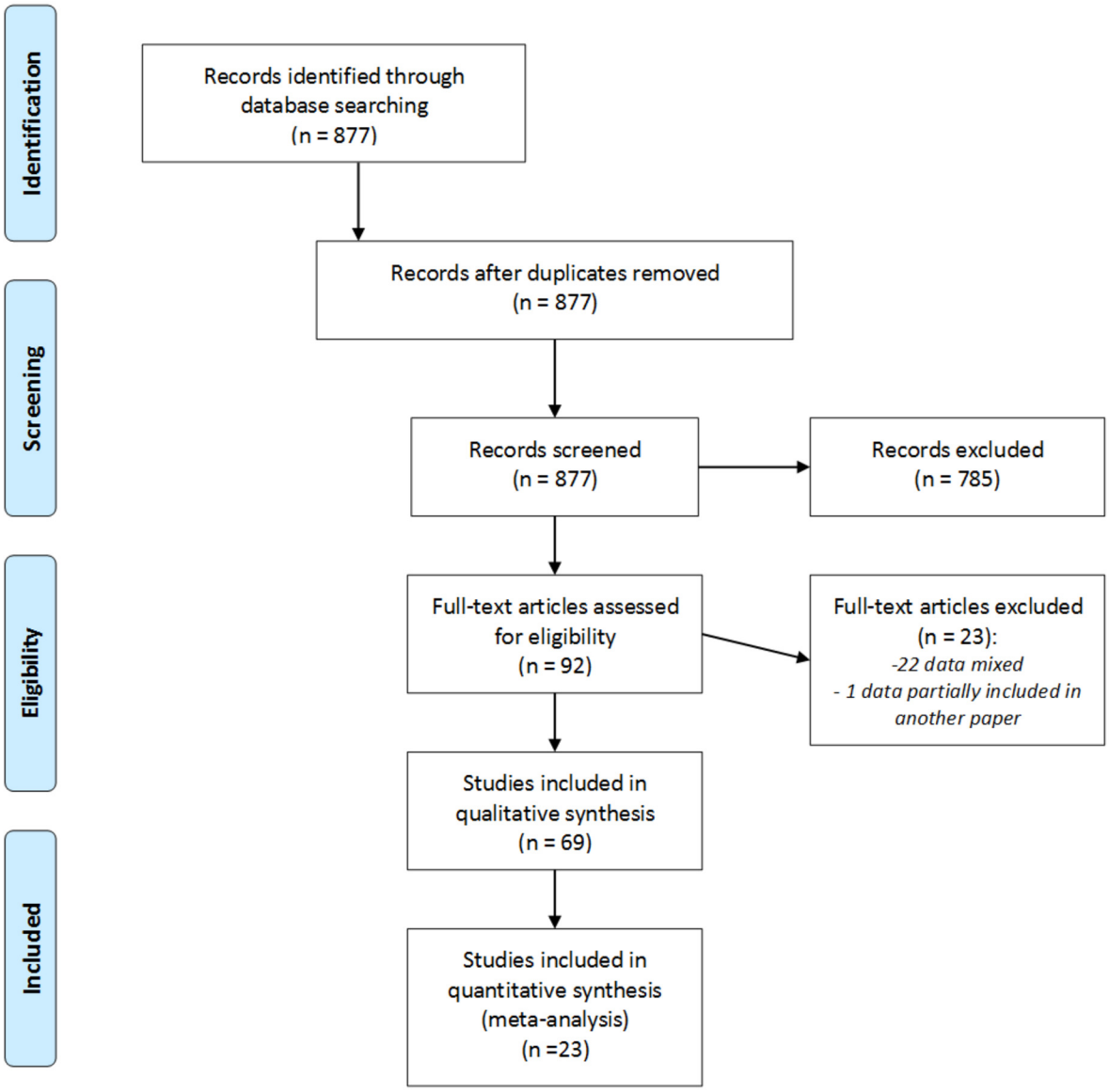
DUS=Duplex UltraSound; y=yes; n=no.

Table II. Fixed effect and random effect models of the variables analyzed in the studies included at quantitative evaluation. The chosen model is represented in bold for each variable. In the last column, the P value indicates the linear regression test of funnel plot asymmetry (efficient score).

Variable of interest	Fixed effect model				Random effect model				p-value*
	OR	95%-CI	z value	p-value	OR	95%-CI	z value	p-value	
Female sex	**0.77**	**[0.63; 0.93]**	**-2.70**	**0.006**	0.79	[0.62; 1.00]	-1.91	0.05	0.11
Age	3.67	[2.09; 5.25]	4.56	<0.0001	**3.54**	**[0.65; 6.43]**	**2.40**	**0.01**	0.94
Obesity	**1.42**	**[1.01; 1.99]**	**2.07**	**0.03**	1.42	[1.01; 2.00]	2.05	0.04	0.34
Active cancer	**1.10**	**[0.79; 1.52]**	**0.59**	**0.55**	1.20	[0.86; 1.68]	1.09	0.27	0.93
active smoke	**0.95**	**[0.64; 1.40]**	**-0.24**	**0.80**	0.99	[0.66; 1.47]	-0.03	0.97	0.96
Immobilization/recent surgery	**1.55**	**[0.94; 2.57]**	**1.73**	**0.08**	1.46	[0.61; 3.52]	0.86	0.39	0.78
Hypertension	1.31	[1.08; 1.59]	2.83	0.004	**1.28**	**[0.98; 1.68]**	**1.86**	**0.06**	**0.74**
Dyslipidemia	**0.92**	**[0.68; 1.26]**	**-0.48**	**0.63**	0.92	[0.68; 1.26]	-0.46	0.64	0.42
COPD	**0.84**	**[0.57; 1.25]**	**-0.84**	**0.40**	0.89	[0.60; 1.34]	-0.52	0.60	0.61
Diabetes	**0.87**	**[0.69; 1.08]**	**-1.21**	**0.22**	0.88	[0.69; 1.11]	-1.03	0.30	0.13
CAD	**1.04**	**[0.79; 1.38]**	**0.33**	**0.74**	1.08	[0.80; 1.46]	0.54	0.58	0.65

CKD	**0.92**	**[0.64; 1.31]**	**-0.45**	**0.65**		0.94	[0.66; 1.35]	-0.31	0.75	0.79
CRP	0.75	[0.07; 1.44]	2.18	0.02		**1.66**	**[-0.35; 3.69]**	**1.61**	**0.10**	**0.44**
D-dimer	**956.86**	**[225.67; 1688.05]**	**2.56**	**0.01**		956.86	[225.67; 1688.05]	2.56	0.01	0.065
Platelets count	**10.13**	**[-12.31; 32.58]**	**0.88**	**0.37**		9.24	[-23.51; 42.00]	0.55	0.58	0.96

OR= Odds Ratio; CI= Confidence Interval; COPD= Chronic Obstructive Pulmonary Disease; CAD= Coronary Artery Disease; CKD= Chronic Kidney Disease; CRP= C-Reactive Protein



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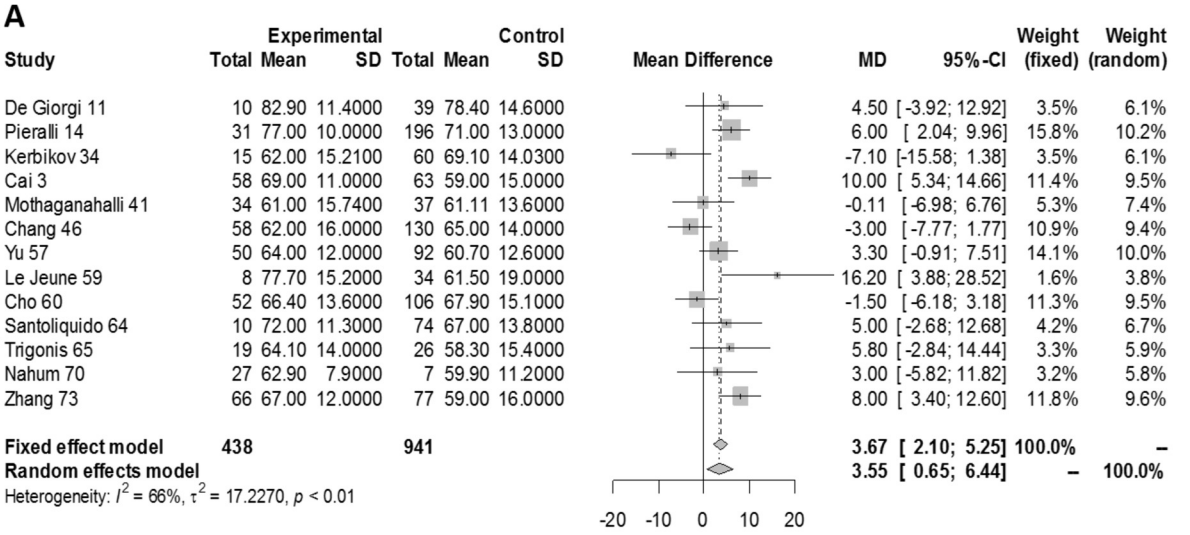

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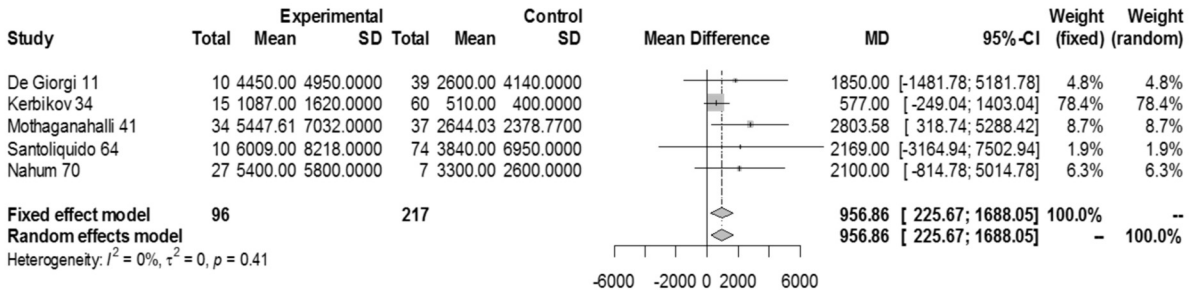

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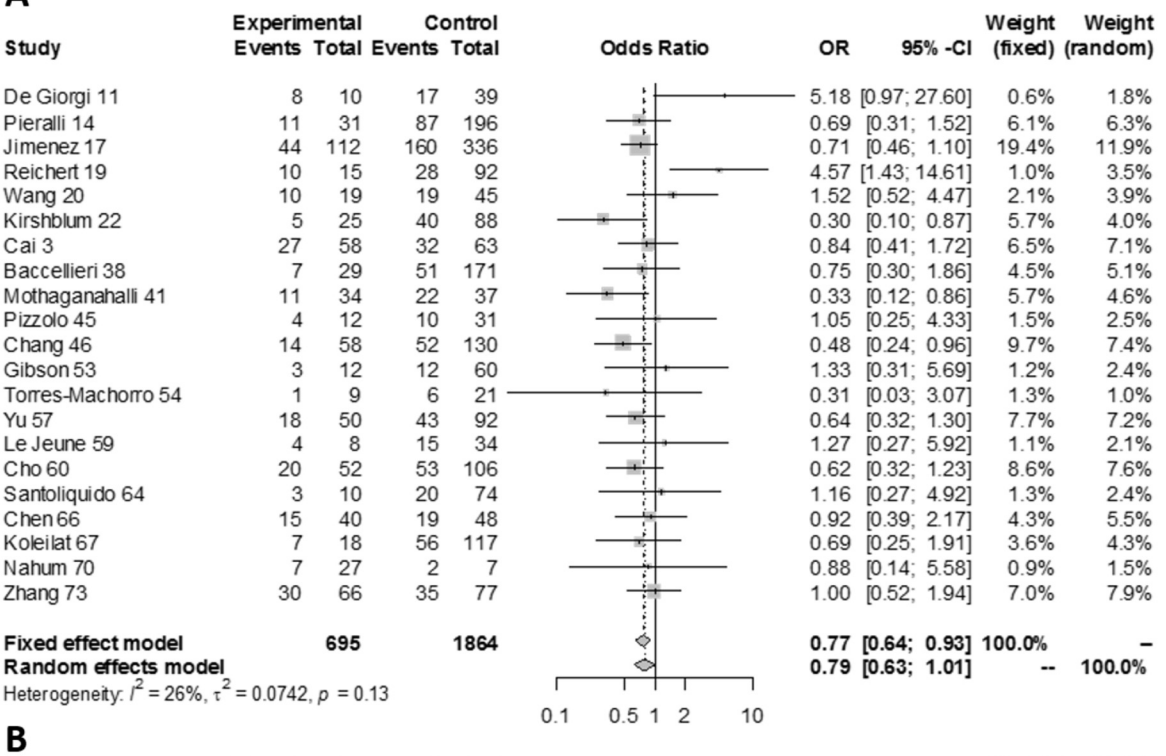

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