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Short communication

Frequency of five cardiovascular/hemostatic entities as primary manifestations of SARS-CoV-2 infection: Results of the UMC-19-S_2

Òscar Miró [a,*], Pere Llorens [b], Sònia Jiménez [a], Pascual Piñera [c], Guillermo Burillo-Putze [d], Alfonso Martín [e], Francisco Javier Martín-Sánchez [f], Juan González del Castillo [f], , on behalf of the Spanish Investigators on Emergency Situations TeAm (SIESTA) network:

Òscar Miró [a], Sònia Jiménez [a], Juan González del Castillo [b], Francisco Javier Martín-Sánchez [b], Pere Llorens [c], Guillermo Burillo-Putze [d], Alfonso Martín [e], Pascual Piñera Salmerón [f], Fahd Beddar Chaib [g], Enrique del Hoyo Peláez [g], Belén Rodríguez Miranda [h], Alejandra Sánchez Arias [h], Noemí Ruiz de Lobera [i], Marta Iglesias Vela [j], Laura Hernando López [j], Carmen del Arco Galán [k], Guillermo Fernández Jiménez [k], E. Jorge García Lamberechts [l], Marcos Fragiel [l], María Jesús Domínguez [m], María Eugenia Barrero Ramos [m], José María Ferreras Amez [n], Belén Arribas Entrala [n], Ángel García García [o], Marta Fuentes de Frutos [o], Ricardo Calvo López [p], Javier Jacob-Rodríguez [q], Ferrán Llopis-Roca [q], María Carmen Ponce [r], Napoleón Meléndez [s], María José Fortuny Bayarri [t], Francisco José Salvador Suárez [t], María Luisa López Grima [u], Mª. Ángeles Juan Gómez [u], Javier Millán [v], José A. Sánchez Nicolás [w], Paula Lázaro Aragües [w], Francisco Javier Lucas-Imbernón [x], Francisco Javier Lucas-Galán [x], Blas Jiménez [y], Blas Jiménez [z], Rigoberto del Río [z], Lluís LLauger García [aa], Begoña Espinosa [ab], Ana Belén Payá [ab], Juan Miguel Porrino [ac], María Rosales Maestre [ac], María José Cano Cano [ad], Rosa Sorando Serra [ad], Carlos Cardozo [ae], Juan José López Díaz [af], Martín Ruiz Grinspan [ag], Cristóbal M. Rodríguez Leal [ag], Sara Gayoso Martín [ah], Silvia Ortiz Zamorano [ah], María Pilar López Díaz [ai], Carmen Agüera Urbano [aj], Elisa Delgado Padial [aj], Ana Peiró Gómez [ak], Elena Gonzalo Bellver [ak], Laura Ejarque Martínez [al], Maribel Marzo Lambíes [al], José Noceda [am], José Vicente Brasó Aznar [an], José Luis Ruiz López [an], Alfons Aguirre Tejedo [ao], Isabel Cirera Lorenzo [ao], Alejandro Martín Quirós [ap], Elena Muñoz del Val [ap], Enrique Martín Mojarro [aq], Brigitte Silvana Alarcón Jiménez [aq], Virginia Carbajosa [ar], Susana Sánchez Ramón [ar], Matilde González Tejera [as], Pablo Herrero Puente [at], Desire María Velarde Herrera [at], Francisco Javier Teigell Muñoz [au], Juan Carlos Repáraz González [au], Félix González Martínez [av], Diana Moya Olmeda [av], Anna Palau [aw], Patricia Eiroa Hernández [ax], Marcos Expósito Rodríguez [ax], Nieves López Laguna [ay], María García-Uría [ay], Josep Guardiola [az], Polo Higa Sansome [az], María José Marchena González [ba], EissaJaloud Saavedra [ba], María Adroher [bb], Ester Soy Ferrer [bb], Arturo Huertas [bc], Raquel Torres Gárate [bd], Beatriz Valle Borrego [bd], Josep María MòdolDeltell [be], Samuel Olmos Soto [be], Elena Díaz Fernández [bf], José Pavón Monzo [bg], Nayra Cabrera González [bg], Ricardo Juárez [bh], Jorge Pedraza García [bi], Manuel Salido [bi], Miguel Moreno Fernández [bj], Carles Pérez [bk], María Teresa Maza Vera [bl], Raquel Rodríguez Calveiro [bl], Josep Tost [bm], Antonio Barceló [bn], Rosario Carrió [bo], Eva Quero Moto [bp]

[a] *Hospital Clínic, Barcelona, Spain*
[b] *Hospital Clínico San Carlos, Madrid, Spain*
[c] *Hospital General de Alicante, Spain*
[d] *Hospital Universitario de Canarias, Tenerife, Spain*
[e] *Hospital Universitario Severo Ochoa de Leganés, Madrid, Spain*
[f] *Hospital General Universitario Reina Sofía, Murcia, Spain*
[g] *Complejo Asistencial de Soria, Spain*

* Corresponding author at: Emergency Department, Hospital Clínic, Villarroel 170, 08036 Barcelona, Catalonia, Spain.
E-mail address: omiro@clinic.cat (Ò. Miró).

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[h] Hospital Universitario Rey Juan Carlos, Madrid, Spain
[i] Hospital San Pedro, Logroño, Spain
[j] Hospital de León, Spain
[k] Hospital de la Princesa, Madrid, Spain
[l] Hospital Clínico San Carlos, Madrid, Spain
[m] Hospital de Fuenlabrada, Madrid, Spain
[n] Hospital Clínico Universitario Lozano Blesa, Spain
[o] Hospital Clínico Universitario de Salamanca, Spain
[p] Complejo Hospitalario Universitario de A Coruña, Spain
[q] Hospital Universitario de Bellvitge de l'Hospitalet de Llobregat, Barcelona, Spain
[r] Hospital de la Vega Baja de Orihuela, Alicante, Spain
[s] Hospital Virgen de los Lirios de Alcoy, Alicante, Spain
[t] Hospital Francesc de Borja de Gandia, Valencia, Spain
[u] Hospital Doctor Peset, Valencia, Spain
[v] Hospital la Fe, Valencia, Spain
[w] Hospital Reina Sofía, Murcia, Spain
[x] Hospital General de Albacete, Spain
[y] Hospital del Vinalopó de Elche, Alicante, Spain
[z] Hospital de Torrevieja, Alicante, Spain
[aa] Hospital Universitari de Vic, Barcelona, Spain
[ab] Hospital General de Alicante, Spain
[ac] Hospital Marina Baixa de Villajoyosa, Alicante, Spain
[ad] Hospital Arnau de Vilanova, Valencia, Spain
[ae] Hospital Clínic de Barcelona, Spain
[af] Hospital Universitario LucusAugusti, Lugo, Spain
[ag] Hospital de Henares, Madrid, Spain
[ah] Hospital Comarcal El Escorial, Madrid, Spain
[ai] Hospital Universitario de Burgos, Spain
[aj] Hospital Costa del Sol de Marbella, Málaga, Spain
[ak] Hospital de Lliria, Valencia, Spain
[al] Hospital de Requena, Valencia, Spain
[am] Hospital Clínico de Valencia, Spain
[an] Hospital Universitario La Ribera, Valencia, Spain
[ao] Hospital del Mar, Barcelona, Spain
[ap] Hospital Universitario La Paz, Madrid, Spain
[aq] Hospital Santa Tecla, Tarragona, Spain
[ar] Hospital Rio Hortega, Valladolid, Spain
[as] Hospital General de Elche, Alicante, Spain
[at] Hospital Universitario Central Asturias, Oviedo, Spain
[au] Hospital de Parla, Madrid, Spain
[av] Hospital Virgen de la Luz, Cuenca, Spain
[aw] Hospital Joan XXIII, Tarragona, Spain
[ax] Hospital Universitario de Canarias, Tenerife, Spain
[ay] Clínica Universidad Navarra, Madrid, Spain
[az] Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
[ba] Hospital Juan Ramón Jiménez, Huelva, Spain
[bb] Hospital Doctor Josep Trueta, Girona, Spain
[bc] Clínica Sagrada Familia, Barcelona, Spain
[bd] Hospital Severo Ochoa de Leganés, Madrid, Spain
[be] Hospital GermansTrias i Pujol de Badalona, Barcelona, Spain
[bf] Hospital Universitario Sant Joan, Alicante, Spain
[bg] Hospital Doctor Negrín, Las Palmas de Gran Canaria, Spain
[bh] Hospital Nuestra Señora del Prado de Talavera de la Reina, Toledo, Spain
[bi] Hospital Valle de los Pedroches de Pozoblanco, Jaén, Spain
[bj] Hospital Regional Universitario de Málaga, Spain
[bk] Hospital Lluís Alcanyís de Xàtiva, Valencia, Spain
[bl] Hospital Álvaro Cunqueiro de Vigo, Pontevedra, Spain
[bm] Consorci Hospitalari de Terrassa, Barcelona, Spain
[bn] Hospital de Denia, Alicante, Spain
[bo] Hospital de Gijón, Asturias, Spain
[bp] Hospital Virgen de la Arrixaca, Murcia, Spain

[a] Emergency Department, Hospital Clínic, IDIBAPS, University of Barcelona, Barcelona, Catalonia, Spain
[b] Emergency Department, Hospital General de Alicante, University Miguel Hernández, Elche, Alicante, Spain
[c] Emergency Department, Hospital General UniversitarioReina Sofía, Murcia, Spain
[d] Emergency Department, Hospital Universitario de Canarias, Tenerife, Spain
[e] Emergency Department, Hospital UniversitarioSevero Ochoa, Universidad Alfonso X, Madrid, Spain
[f] Emergency Department, Hospital Clínico San Carlos, IDISSC, Univesdad Complutense, Madrid, Spain

1. Introduction

Infection by SARS-Cov-2 is mainly characterized by fever and respiratory symptoms, with dyspnea and lung infiltrates in more severe cases [1,2]. Many patients also present a pro-coagulant state, which is biochemically detected by increased D-dimer levels and is related to complications and a worse prognosis [1,3]. In this context, isolated case reports and short case series have suggested an increased risk of patients with COVID-19 to develop clinically relevant cardiovascular and hemostatic disturbances [3–7]. Nonetheless, many of these reports refer to hospitalized patients, and as hospitalization itself usually increases complications in bedridden patients with multidrug treatment

or in very poor condition, it is unknown if such cardiovascular/hemostatic processes are related to the pathogenesis of SARS-Cov-2. Focus on patients with COVID-19 at emergency department (ED) arrival could help to answer this question.

2. Methods

The UMC-19 (Unusual Manifestations of Covid-19) is a retrospective, multicenter, case-control, multipurpose project based on review of medical reports of patients attended at Spanish EDs seeking 10 processes that could eventually be increased by SARS-CoV-2. Details of the whole project have been previously published[6]. Five of these unusual manifestations correspond to cardiovascular/hemostatic disturbances: acute coronary syndrome (ACS), deep venous thrombosis (DVT), pulmonary embolism (PE), stroke and upper gastrointestinal bleeding (UGB). Study 2 (UMC-19-S_2) was designed to analyze the frequency of these five cardiovascular/hemostatic manifestations in COVID patients attending EDs (cases) and compare these frequencies with those observed in the overall ED population (non-COVID patients, controls). Cases were all patients diagnosed with COVID-19 (either, microbiologically or clinically) between March 1st and April 30th, 2020 in the participating EDs (during this 61-day period, 213,435 cases of COVID-19 were confirmed in Spain). Controls were all non-COVID patients coming to EDs in a 2-month period (COVID period) and all patients consulting the ED between March 1st and April 30th, 2019 (pre-COVID period). Cardiovascular/hemostatic manifestations in cases and controls were first identified through the electronic system according to specific codes and were then manually reviewed in medical reports and confirmed by the principal investigator of each center. ACS included both myocardial infarction with or without ST elevation, and stroke included both ischemic and hemorrhagic events. The complete methodology has been extensively detailed elsewhere [8,9].

The relative frequency of the 5 above mentioned cardiovascular/hemostatic entities in ED comers in cases and controls was compared following two different strategies: 1) by comparing the relative frequency in COVID patients using non-COVID patients as comparator (altogether and also using the subgroups of non-COVID patients included in 2019 and 2020 separately); and 2) by comparing the relative frequency in 2020 with respect to 2019. In order to describe the main baseline patient characteristics, we collected age, sex and comorbidities for all cases presenting any of the 5 entities, and compared them with a sample of controls recruited by randomly selecting one control (1: 1) with the same diagnosis from the entire list of controls. Comparisons were performed using the chi square or ANOVA test, as needed.

3. Results

The case group included 63,822 COVID patients diagnosed in 50 Spanish EDs. In this group, we identified 99 ACS (incidence: 1.55‰, 95% confidence interval [CI]: 1.26- 1.89), 69 DVT (1.08‰, 1.57- 1.72), 353 PE (5.53‰, 4.97–6.14), 134 strokes (2.11‰, 1.77–2.49; 85% ischemic and 15% hemorrhagic) and 73 UGB (1.14‰, 0.90- 1.44). SARS-CoV-2 infection was demonstrated in 76% of these cases by polymerase chain reaction (PCR) in nasopharyngeal swear, while diagnosis was established based on signs/symptoms of COVID-19 and/or in typical chest X-ray or computerized tomography findings in the remaining 24%, taking into account the epidemiological context of the enormous number of people infected by SARS-CoV-2 and the shortage of PCR tests experienced worldwide in March–April 2020. The control group included 1,125,491 non-COVID patients (pre-COVID period: 782,125; COVID period: 343,366), with 2701 ACS (3.55‰, 3.44–3.66), 1,147 DVT (1.64‰, 1.57- 1.72), 766 PE (1.23‰, 1.16 - 1.0.29), 2995 strokes (4.43‰, 4.31–4.55; 86% ischemic, 14% hemorrhagic) and 1,371 UGB (1.94‰, 1.86–2.03). There were few differences in the age demographic data and comorbidities of cases and controls presenting cardiovascular/hemostatic manifestations (Table 1). Remarkably, COVID patients with UGB and ACS were older than non-COVID patients, and those with PE were younger. Additionally, COVID patients with PE were less frequently women and less frequently had active cancer.

According to relative frequencies, PE was more frequent in COVID than in non-COVID patients in the ED (odds ratio: 4.53, 95% CI: 4.03-5.10), while ACS, DVT, stroke and UGB were significantly less frequent (0.44, 0.36–0.53; 0.66, 0.52–0.84; 0.47, 0.40–0.56; and 0.59, 0.47–0.74; respectively). Similar results were found comparing COVID patients with non-COVID patients recruited during the pre-COVID and the COVID periods separately (Fig. 1). When comparing the relative frequencies of the five cardiovascular/hemostatic manifestations in EDs comers of 2020 with those of 2019, PE was markedly and significantly increased (OR = 2.13, 95%CI= 1.95–2.32), and DVT, stroke and UGB showed less marked, albeit also statistically significant, increments (OR= 1.33, 95%CI= 1.27- 1.40; OR= 1.27, 95%CI= 1.17 - 1.0.39; and OR= 1.26, 95%CI= 1.17 - 1.0.37; respectively). The relative frequency of ACS was practically identical in 2020 and 2019.

4. Discussion

We quantified the frequency of five cardiovascular/hemostatic manifestations in COVID patients at ED consultation before hospitalization. We acknowledge these relative frequencies do not correspond to the real relative frequency of these entities in the general population as they were obtained in ED comers. On one hand, it should be highlighted that only about 10% of COVID patients consulted the ED during the pandemic in Spain; therefore, incidences could be up to 10 times lower. Nonetheless, it is expected that most of the patients presenting the cardiovascular/hemostatic entities analyzed finally attended an ED for health care. The exception to this assumption is that during the 2020 lockdown patients with mild manifestations might have remained at home [10–12]. On the other hand, manifestations developed during hospitalization were not taken into account, and their inclusion would have led to an (unknown) increase of our estimates. However, these episodes could result from hospitalization complications rather than directly to the pathogenesis of SARS-CoV-19, and additionally, from the selection of the sickest patients who are usually hospitalized. For example, while this study showed a relative PE frequency of 0 5.% (353/63,822) in COVID patients, single center case-series reported a relative PE frequency of 2.6% (10/388) [4] and 8.2% (23/280) 5 in hospitalized patients, and 20.6% (22/107) [6] in patients admitted to intensive care. Remarkably, using the same comparator (non-COVID patients in the ED, altogether or separated by pre-COVID and COVID period ED comers), PE was increased more than 4 fold while the remaining cardiovascular/hemostatic processes decreased by about half. This suggests that PE is probably a highly frequent entity during SARS-CoV-2 infection, being greater than expected in ED populations and also having the highest increased risk among cardiovascular/hemostatic processes.

Our finding of an increased relative frequency of PE during 2020 with respect to 2019 suggests that part of this increase was due to the COVID pandemic. Conversely, the statistically significant increases of UGB, stroke and DVT in 2020 were lower, and the role of SARS-CoV-2 in these increments would not be as clear as in PE. In fact, PE was one of the first systemic complications that clinicians noted in COVID patients [3,6,13], and it is currently a matter of intense research. It has been suggested that some PE in COVID patients could develop in situ in lungs, favored by a highly inflammatory involvement in a pathophysiological process known as “immunothrombosis” [14–16]. In this sense, alveolar injury and the inflammatory storm present during COVID-19 pneumonia along with disruption of the thrombo-protective state of the pulmonary vascular endothelial cells might contribute to the formation of deep small vessel thrombi in the absence of other classical risk factors such as estrogenic treatment, immobilization or cancer. Our finding of a lower increase in DVT than in PE in COVID patients, as well as the significantly lower frequency of women and cancer in PE

Table 1
Comparison between cases and controls that developed one of the five cardiovascular/hemostatic entities analyzed in the UMC-19-S_2 study. Comparisons were made in 73 pairs of COVID and non-COVID patients with upper gastrointestinal bleeding, 134 pairs with stroke, 353 pairs with pulmonary embolism, 69 pairs with deep venous thrombosis, and 99 pairs with acute coronary syndrome.

	Upper gastrointestinal bleeding (COVID/non-COVID)	Stroke (COVID/non-COVID)	Pulmonary embolism (COVID/non-COVID)	Deep venous thrombosis (COVID/non-COVID)	Acute coronary syndrome (COVID/non-COVID)
Age [mean (SD)]	77 (15) vs 70 (17)	74 (13) vs 76 (12)	**65 (16) vs 68 (17)**	69 (15) vs 65 (19)	**75 (13) vs 66 (14)**
	$P = 0.020$	$P = 0.215$	***P* = 0.026**	$P = 0.170$	***P* < 0.001**
Female	38% vs 41%	49% vs 40%	**42% vs 53%**	44% vs 51%	31% vs 32%
	$P = 0.735$	$P = 0.179$	***P* = 0.007**	$P = 0.394$	$P = 0.879$
Hypertension	66% vs 62%	65% vs 75%	47% vs 52%	58% vs 46%	81% vs 65%
	$P = 0.606$	$P = 0.084$	$P = 0.287$	$P = 0.173$	$P = 0.011$
Dyslipidemia	43% vs 38%	46% vs 53%	39% vs 36%	29% vs 28%	58% vs 50%
	$P = 0.613$	$P = 0.272$	$P = 0.971$	$P = 0.850$	$P = 0.254$
Diabetes mellitus	32% vs 23%	29% vs 31%	18% vs 16%	13% vs 10%	32% vs 28%
	$P = 0.266$	$P = 0.789$	$P = 0.535$	$P = 0.595$	$P = 0.536$
Obesity (clinically estimated)	15% vs 22%	13% vs 17%	15% vs 18%	23% vs 19%	18% vs 21%
	$P = 0.286$	$P = 0.396$	$P = 0.267$	$P = 0.531$	$P = 0.592$
Coronary artery disease	14% vs 7%	18% vs 13%	6% vs 5%	4% vs 3%	47% vs 38%
	P = 0.173	0.313	$P = 0.589$	$P = 0.649$	$P = 0.250$
Chronic heart failure	11% vs 15%	10% vs 11%	3% vs 5%	1% vs 9%	16% vs 8%
	0.461	$P = 0.690$	$P = 0.118$	$P = 0.052$	0.082
Chronic obstructive pulmonary disease	15% vs 8%	10% vs 12%	7% vs 11%	4% vs 12%	14% vs 14%
	$P = 0.197$	$P = 0.555$	$P = 0.058$	$P = 0.116$	$P = 1{,}000$
Active cancer	19% vs 15%	13% vs 19%	**13% vs 26%**	15% vs 16%	12% vs 14%
	$P = 0.372$	0.187	**p < 0.001**	$P = 0.813$	$P = 0.674$
Dementia	18% vs 10%	13% vs 9%	7% vs 9%	7% vs 7%	9% vs 6%
	$P = 0.149$	$P = 0.245$	$P = 0.325$	$P = 1.000$	$P = 0.420$

Bold numbers denote comparisons being statistically significant ($p < 0.05$).

in COVID patients respect to PE in non-COVID patients would suggest such hypothesis.

Some limitations impose caution in interpreting our findings. In many cases the diagnosis was based on clinical/radiological findings, with no microbiological confirmation, although this was the rule in Spanish (and many countries) EDs due to test shortage [17,18]. During the COVID-19 pandemic, emergency physicians have had a lower threshold for ordering some diagnostic studies (computerized tomography

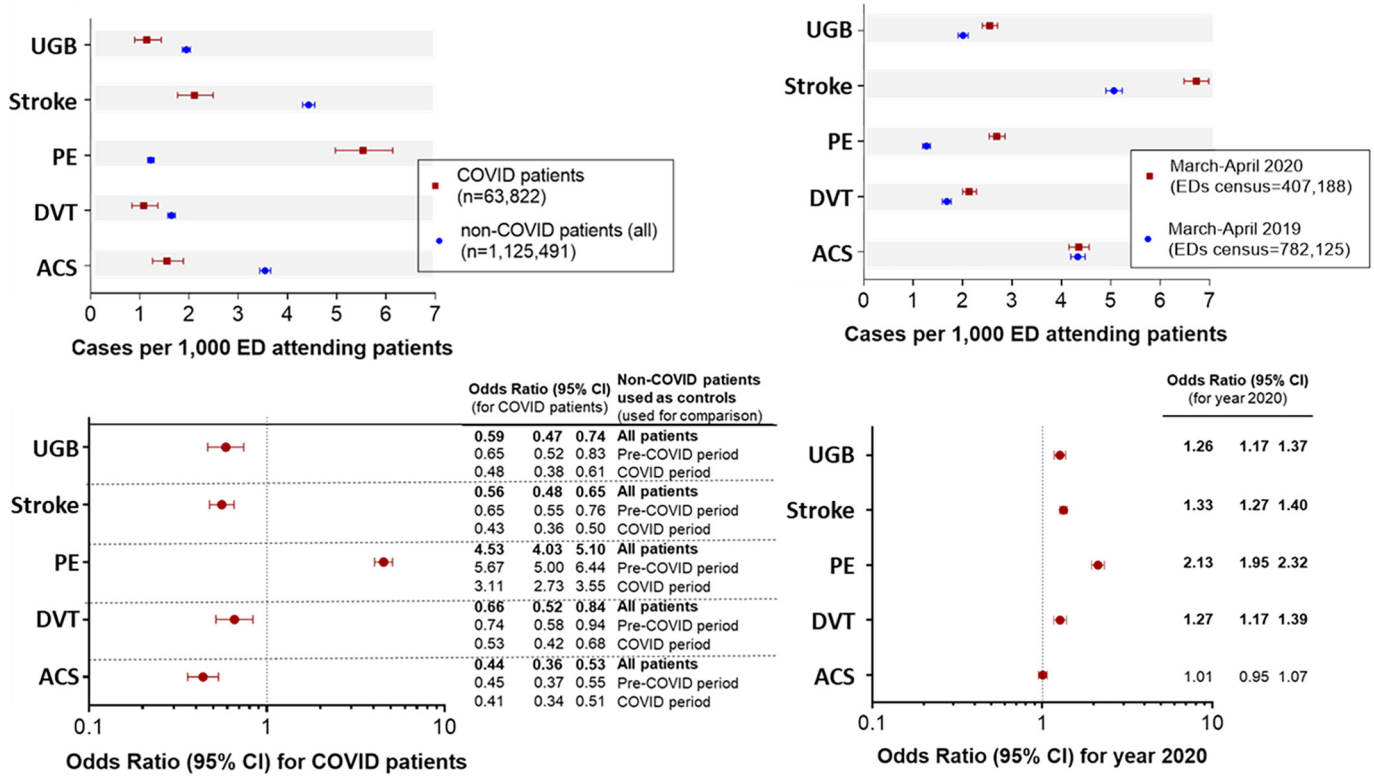

Fig. 1. Comparison of frequency of the five cardiovascular/hemostatic entities assessed in the UMC-19-S_2 study in COVID-19 and non-COVID patients attending emergency departments (upper panel) and odds ratios for COVID with respect to non-COVID patients (lower panel; graph on the left represents only odds ratios obtained from comparison with all non-COVID control patients, while odds ratios obtained from separate comparison with non-COVID patients coming from the pre-COVID and the COVID periods are presented in the table at the right). UGB: upper gastrointestinal bleeding; PE: pulmonary embolism; DVT: deep venous thrombosis; ACS: acute coronary syndrome.

pulmonary angiograms, Doppler ultrasonography), and the number of diagnosis could actually have been higher. Patient-related or disease-related factors could, to some extent, have accounted for decreased/increased relative frequencies, and we did not adjust for them. Finally, ED patients and disease typology could have differed during the COVID outbreak (due to country lockdown), although the similar rates observed for COVID patients for the five cardiovascular/hemostatic manifestations using both subgroups of controls (from the pre-COVID and the COVID periods) do not support this possibility. In addition, by comparing rates between 2020 and 2019, the relative frequency of PE among ED comers remained overtly increased.

Despite all these limitations, the UMC-19-S_2 study shows that PE was clearly increased in ED comers during the 2020 period, suggesting that this increase may be linked to SARS-CoV-2 infection. The role of SARS-CoV-2 in the mild increments observed in DVT, stroke and UGB needs to be further investigated.

Authors contribution

All authors discussed the idea and design of study and provided patients. Data analysis and first draft writing was done be OM. All authors read such a draft and provided insight for the final version. OM is the guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article.

Declaration of Competing Interest

None author reported any conflict of interest directly or indirectly connected with this manuscript.

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